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Section Health Technology Assessment

Health Technology Assessment (HTA)

HTA Report

Title	Three-monthly vs monthly use of bone-targeting agents in patients with bone metastases
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Technology	Bone-targeting agents (zoledronate, ibandronate, denosumab)
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Executive Summary:

BACKGROUND: Zoledronate, ibandronate, and denosumab are licensed bone-targeting agents (BTAs) in Switzerland. Patients with bone metastases are treated monthly with BTAs to reduce fracture risk and hypercalcaemia. Long-term exposure to BTAs is linked to possible severe side effects such as hypocalcaemia, renal failure, or cumulative risk of osteonecrosis of the jaw (ONJ). Recent studies suggest that reduced treatment frequency is as efficacious as the current monthly therapy. Consequently, the question arises as to whether the monthly administration of BTAs in patients with bone metastases should be replaced by a 3-monthly administration.

OBJECTIVE: The objective of this health technology assessment (HTA) was to assess the evidence pertaining to 3-monthly versus 1-monthly administration of BTAs in cancer patients with bone metastases in terms of efficacy, effectiveness, and safety, as well as cost, cost-effectiveness, budget impact, legal, social, ethical, and organisational issues.

METHODS: A systematic literature search was conducted for all the HTA domains using Medline, Embase, Evidence-Based Medicine Reviews, and Cochrane Central Register of Controlled Trials on January 18, 2021. Outcomes of interest (skeletal-related events [SREs] and adverse events [AEs]) were synthesized in a meta-analysis. A random effects (RE) model was used for the main analysis due to the limited number of included studies. A cost-comparison model and a budget impact model were developed to evaluate economic parameters.

RESULTS:

Efficacy, effectiveness, and safety

In total, 5,375 records were identified in the literature search. For zoledronate and denosumab, 7 unique randomized controlled trials (RCTs) from 9 publications and 2 retrospective studies were eligible for inclusion. No studies were found for ibandronate. The risk of bias assessment found the studies to be of moderate to low risk of bias.

For the meta-analysis, data from 6 RCTs reporting on SREs (4 zoledronate, n=2,668; 2 denosumab, n=160) were included to help answer the research question. The results from the meta-analyses applying the RE model showed no statistically significant effect between both dosing regimens for SREs, AEs, or SAEs. The result for SREs was a risk ratio (RR) of 1.01; 95% confidence interval (CI): 0.82, 1.24 with the RE model. These results indicate SREs may decrease by up to 18% or increase by 24% when 3-monthly dosing is used compared to monthly dosing. Heterogeneity was low (I^2=0%).

The RR result for AEs with RE model was: RR: 0.97; 95% CI: 0.93, 1.02 in the main analyses. The results suggest that 3-monthly use of BTAs may lead to a reduction in AEs of up to 7% or up to a 2% increase. Heterogeneity between the studies was low (I^2=0%). The results indicated no difference in SAEs and AEs of special interest in this indication, like hypocalcaemia, ONJ, or renal AEs. The SAE RE model CIs showed a potential decreased risk of 21% vs a potential increased risk of 9% (RR: 0.93; 95% CI: 0.79, 1.09). Thus, a 3-monthly administration may lead to a benefit in reducing SAEs by up to 21% while increasing SREs by up to 24%.

Sensitivity analyses assessing the single BTAs separately and including non-RCTs largely confirmed the results from the main analyses.

Cost, cost-effectiveness, and budget impact

One cost-effectiveness study retrieved from the literature search was eligible for inclusion. Findings of this United States (US) study could not be transferred to the Swiss context due to the differences in treatment costs. Therefore, a de novo budget impact and cost-comparison model from a payer perspective were developed.

The base case budget impact and cost-comparison model accounted for drug costs, administration costs, and treatment discontinuation costs. The cost comparison model is at the single patient level, whereas the budget impact model is at the national level, considering the size of the population eligible for treatment. It is assumed that patients already on treatment will not change their regimen and, as a result, the 3-monthly treatment interval is only relevant for new patients.

The incidence of patients with bone metastases and currently on BTA treatment is approximately 2,497 patients, and it was estimated that 15,365 patients would require BTA treatment in year 5. Over this time horizon, the introduction of 3-monthly treatment for patients with bone metastases, instead of the monthly dosing, would result in a reduction in the total budget impact of CHF 53,170,447 (base case). Annually, the reductions in budget impact were CHF 6,747,073 (year 1) up to CHF 12,713,068 (year 5). Univariate sensitivity analyses were conducted to test the sensitivity of the model variations in the model parameters by varying individual parameters over a range between ±10%. Results were most sensitive to the number of eligible incident patients. The cost-comparison model showed an average cost reduction of CHF 2,675 and CHF 988 per patient in the first and fifth year, respectively. In total, a cost reduction of CHF 8,326 per patient was observed over the 5-year time horizon.

Legal, social, ethical, and organisational issues

No evidence was identified for these HTA domains.

CONCLUSION: Whilst evidence to evaluate the use of BTAs with different administration frequencies in cancer patients with bone metastases is limited, meta-analyses of available trial data indicate that the 3-monthly administration of BTAs in cancer patients with bone metastases is associated with a similar risk of SREs, AEs, and SAEs as monthly administration of these BTAs. A longer dosing interval leads to a reduction in treatment cost over a 5-year time horizon. Given the similarity in efficacy/effectiveness and safety, extended-interval dosing of BTAs may lead to a substantial reduction in annual direct costs per patient and, ultimately, in the annual budget impact in Switzerland. Evidence to evaluate the use of BTAs with different administration frequencies in cancer patients with bone metastases remains scarce, limiting the ability to draw definitive conclusions.

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Abbreviations and acronyms

AE	adverse event
AL	medical performance
ATC	anatomical-therapeutic-chemical classification
BC	breast cancer
BM	bone metastasis
BP	bisphosphonate
BPI	Brief Pain Inventory
BTA	bone-targeting agent
CADTH	Canadian Agency for Drugs and Technologies in Health
Ca^{+2}	calcium
CCTR	Cochrane Central Register of Controlled Trials
CDSR	Cochrane Database of Systematic Reviews
CHEC	Consensus Health Economics Checklist
CHF	Swiss franc
CI	confidence interval
CRPC	castration-resistant prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal telopeptide
CTX-I	carboxy-terminal crosslinked telopeptide of collagen type I
DARE	Database of Abstracts of Reviews of Effects
DKK-1	Dickkopf-1
EBMR	Evidence-Based Medicine Reviews
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESAS	Edmonton Symptom Assessment System
EUnetHTA	European Network for Health Technology Assessment
EUR	euro
EXP	exponential function
FE	fixed effects
FEM	fixed effects model
FOPH	Federal Office of Public Health
GP	general practitioner

HAS	Haute Autorité de Santé
HCRU	healthcare resource utilization
HKSJ	Hartung-Knapp-Sidik-Jonkman
HRQoL	health-related quality of life
HTA	health technology assessment
I/C	intervention/comparator
ICER	incremental cost-effectiveness ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	intravenous
KLV	Healthcare Benefits Ordinance
LC	lung cancer
LN	natural logarithm
LY	life-year
LYG	life-year gained
MA	meta-analysis
mBC	metastatic breast cancer
mCRPC	metastatic castration-resistant prostate cancer
mLC	metastatic lung cancer
MM	multiple myeloma
mNSCLC	metastatic nonsmall cell lung cancer
mPC	metastatic prostate cancer
mSCLC	metastatic small cell lung cancer
NA	not applicable
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NPRS	Numeric Pain Rating Scale
NSCLC	nonsmall cell lung cancer
NTX	N-terminal telopeptide
ONJ	osteonecrosis of the jaw
OS	overall survival
P	population
PC	prostate cancer
PICOS	population, intervention, comparator, outcome, study design

PICO (EO)	population, intervention, comparator, outcome (economic outcomes)
PK	pharmacokinetics
QALY	quality-adjusted life-year
QoL	quality of life
RAE	renal adverse event
RANKL	receptor activator of nuclear factor kappa-b ligand
RCT	randomized controlled trial
RE	random effects
RoB	risk of bias
RR	risk ratio
SAE	serious adverse event
SC	subcutaneously
SCLC	small cell lung cancer
SLR	systematic literature review
SmPC	Summary of Medical Product Characteristics
SMR	skeletal morbidity rate
SRE	skeletal-related event
SSE	symptomatic skeletal event
TL	technical performance
TP	Taxpunkt
TPW	Taxpunktwert
US	United States
USD	United States dollar
VRS	Verbal Rating Scale
ZA	zoledronate

Objective of the HTA report

The objective of this health technology assessment (HTA) is to generate a focused assessment of various aspects of 3-monthly vs monthly use of bone-targeting agents (BTAs) in patients with bone metastases. The analytic methods applied to assess the value of using a health technology, their execution, and the results are described. The analytical process is comparative, systematic, and transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety; costs; cost-effectiveness and budget impact; and ethical, legal, social, and organisational issues. The purpose is to inform health policy and decision making to promote an efficient, sustainable, equitable, and high-quality health system.

1 Policy question and context

The BTAs zoledronate, ibandronate, and denosumab are used in cancer patients with bone metastases. In combination with standard antineoplastic therapy, the aim is to reduce the risk of fracture, bone pain, and hypercalcaemia. However, long-term exposure to these agents is associated with potentially severe side effects, such as hypocalcaemia, renal failure, and cumulative risk for osteonecrosis of the jaw (ONJ). Furthermore, there are studies[1 2] suggesting that a reduced frequency dosing might have the same efficacy as the current administration frequency. Consequently, the question is whether the current indication of monthly administration of these 3 BTAs may be replaced by 3-monthly administration. Throughout this document, monthly administration is referring to 3- to 4- weekly administration and 3-monthly administration to 12-weekly administration in accordance with the label of the BTAs and the treatment frequencies in the included studies.

2 Research questions

1) Is 3-monthly administration of BTAs in cancer patients with bone metastases noninferior to monthly administration in terms of clinical efficacy and safety?
    a. Is 3-monthly infusion of the bisphosphonates zoledronate or ibandronate noninferior to monthly infusion (every 3–4 weeks) of zoledronate or ibandronate, respectively, in terms of clinical efficacy and safety?
    b. Is 3-monthly subcutaneous (SC) administration of denosumab noninferior to monthly (every 4 weeks) denosumab SC administration in terms of clinical efficacy and safety?
2) What impact does a 3-monthly administration have compared to monthly administration from an economic, legal, social, ethical, and organisational perspective?

The term “noninferior” is defined as “not worse” in terms of clinical efficacy and safety. A noninferiority trial demonstrates that the test technology (here: administration of BTAs every 3 months) is not less efficacious, effective, and safe within predefined margins than the comparator technology (here: administration of BTAs every month).[3 4]

3 Medical background

3.1 Incidence and prevalence of bone metastases

Bone is the most frequent site of cancer metastases. The relative incidence of bone metastases (BM) in patients with metastatic disease has been reported to be 70% in breast cancer (BC), 85% in prostate cancer (PC), 40% in lung cancer (LC), 40% in kidney cancer, and 95% in multiple myeloma (MM).[5 6] The most common primary cancer forms leading to BM are BC, PC, and LC, accounting for more than 80% of all patients with BM.[4] Of all 19,036 cancer deaths in Switzerland in 2020, 1,506 (7.9%) were associated with BC, 1,299 (6.8%) with PC, and 3,582 (18.8%) with LC. Despite being the cancer type with the highest mortality rate and, thus, rate of metastatic disease, LC was only the third most common cancer after BC and PC in Switzerland in 2020, accounting for 7.5% of all cancers. BC and PC, accounting for 12.1% and 11.1% of all cancers in 2020, respectively, have the highest 5-year prevalence rates among all cancers.[7]

3.2 Disease description

Bone is the stabilizing framework of the body and is formed by osteoblasts and osteoclasts. During bone development, osteoclasts disassemble and resorb old bone cells while osteoblasts built up new bone; thus, these processes require tight regulation of bone remodelling.

Two mechanisms contribute to malignant bone involvement of cancer patients. First, cancer cells can stimulate osteoclasts to increase osteoclast differentiation and activity while simultaneously inhibiting osteoblasts. This leads to higher resorption rates of bone cells without new ones being built up, which results in bone degradation and the formation of osteolytic lesions. In consequence, the bone structure is destabilized and weakened so the bone can break more easily. Second, stimulation of osteoblasts by cancer cells might lead to increased cell growth without older bone cells being resorbed first. Although this process hardens the bone, blastic lesions and sclerosis can occur, also causing the affected bone to break more easily than normal bone. Thus, BM are classified as osteolytic, osteoblastic, or mixed according to the primary mechanism of interference with normal bone remodelling.[5 8] Osteolytic BM commonly occurs in patients with lung cancer or MM, while osteoblastic BM is often observed in PC patients. In contrast, metastatic BC is associated with the mixed type.[6]

During the processes of bone resorption and bone formation, biochemical markers are released. The release of these bone markers facilitates monitoring the bone turnover, since they reflect the metabolic activities of osteoclasts (resorption) and osteoblasts (formation). Bone formation markers consist of osteoblastic enzymes or byproducts of active osteoblasts, such as propeptide of type 1 procollagen,

while bone resorption markers include mainly byproducts of type I collagen degradation, like N-terminal telopeptide (NTX), noncollagenous bone matrix proteins, or osteoclastic enzymes. Furthermore, regulators of the activity of bone cells, such as receptor activator of the nuclear factor kappa B ligand (RANKL), may be used as biomarkers. Some studies suggest that the level of bone markers in blood or urine are predictive for the efficacy of BM treatment. However, their role in routine clinical practice is still unclear.[9]

Although for many types of cancer (e.g., BC, PC), survival with BM is better compared to survival with, for example, metastases in the liver, the presence of BM significantly affects patient morbidity. BM often lead to skeletal-related complications, such as painful pathologic fractures and other, mostly painful, bone-related events. Skeletal-related trial endpoints are composite measures of events collectively termed skeletal-related events (SREs). SREs are defined as pathologic fractures, spinal cord compression, necessity for radiation to bone (for pain or impending fracture), or surgery to bone.[10 11]

Pathological fractures occur in 10% to 30% of all cancer patients, with proximal parts of the long bones being the most frequent fracture site and the femur accounting for over half of all cases.[12] Pathologic fractures due to BM are especially reported for patients with BC, accounting for 60% of pathological fractures and leading to impaired mobility and suffering of pain.[12 13]

Bone pain from BM is caused by inflammatory or mechanical reasons like fractures and is one of the most common types of pain from cancer. Bone pain is poorly localized, worse at night, and not necessarily relieved with sleep or lying down.[14] Back pain caused by spinal cord compression is most commonly reported for BC (20%–30%) and LC (15%).[5]

Bone marrow infiltration may result in bone marrow aplasia and hypercalcaemia, the latter being the most common metabolic complication of the disease.[15] In the final stages, cancer-induced hypercalcaemia can lead to cardiac arrhythmias, acute renal failure, severe neurological impairment, and death.[15 16]

Due to pain, impaired general health status, and restricted physical abilities, BM not only affect the morbidity of cancer patients but also significantly reduce their quality of life (QoL).[17]

As up to 75% of cancer patients with metastases may eventually develop BM, treatment of these patients is an important health issue in Switzerland.[18]

3.3 Diagnosis and treatment of bone metastases

In potential cases of BM, basic screening needs to be performed when one of the signs and symptoms described in Section 3.2 is present: a complete blood cell count to evaluate for anaemia and

myelosuppression and serum calcium, phosphorus, 25-hydroxyvitamin D, alkaline phosphatase, creatinine, thyroid-stimulating hormone, protein electrophoresis and, in some cases, parathyroid hormone level to identify bone turnover and evaluate hypercalcaemia. This must be complemented with imaging data from, for example, radiographs, bone scintigraphy, tomography, and/or magnetic resonance.[5]

The aims of BM treatment are the prevention of disease progression and symptom palliation. Treatment decisions depend on several factors like location and progression of the BM, pre-treatment history, and manifestation of symptoms and general health status. Treatment options include radiotherapy, radioisotope therapy, endocrine therapy, chemotherapy, biologically targeted therapy, immunotherapy, and surgical therapy. However, administration of BTAs, such as zoledronate, ibandronate, or denosumab, is the primary medical treatment choice for the prevention of SREs. These complement cancer-specific treatments by improving bone structure and minimizing the risk of skeletal morbidity.[6 19] An exception to generally treating bone metastases with BTAs is metastatic hormone-sensitive prostate cancer (mHSPC), for which current clinical guidelines do not recommend BTA treatment because several RCTs of BTAs did not show a benefit for these agents in preventing SREs in mHSPC.[20 21] However, BTAs are often used in patients with mHSPC even without a need for osteoporotic fracture prevention, indicating an inappropriate use of BTAs in this patient group.[20]

4 Technology

4.1 Technology description

There are different types of BTAs, including bisphosphonates (BPs) and a human monoclonal antibody targeting RANKL. BPs inhibit osteoclast-mediated bone resorption by binding hydroxyapatite to bone. This leads to the inhibition of hydroxyapatite breakdown and induction of osteoclast apoptosis.[22-24] Furthermore, BPs appear to positively affect osteoblasts by preventing osteocyte and osteoblast apoptosis.[25]

Similarly, the inhibition of the protein RANKL by human monoclonal antibodies reduces the formation and activity of bone-resorbing osteoclasts.[18] In contrast to BPs, these antibodies are not embedded in the bone tissue but rather bind RANKL in the extracellular fluid and circulation.[26] Thereby, the ligand is neutralized and the differentiation of immature cells into osteoclast is inhibited.[27]

In Switzerland, the licensed BTAs are zoledronate (third-generation BP), ibandronate (second-generation BP), and denosumab (RANKL inhibitor). BTAs are administered in patients with BM from solid tumours or in patients with MM to prevent SREs and treat cancer-induced hypercalcaemia. Zoledronate is approved for the prevention of SREs in patients with BM of solid tumours. Ibandronate is

only licensed for BM due to BC. Denosumab is licensed for the treatment of patients with BM of solid tumours in combination with an antineoplastic standard of care.[23 24 28] According to the label, the approved dosing for ibandronate is 6 mg and for zoledronate is 4 mg during an infusion of at least 15 minutes every 3 to 4 weeks.[23 24] The approved dosing for denosumab is 120 mg every 4 weeks for malignant disease metastatic to the bone. It is injected SC.[28 29]

The use of the BPs and denosumab is contraindicated in patients with hypersensitivity to the active substance (or to any of the excipients or to other bisphosphonates) and in pregnant or breast-feeding patients.[23 30] Beyond that, ibandronate is contraindicated in patients with hypocalcaemia and in children and adolescents.[24 31] In the Summary of Medical Product Characteristics (SmPC) from the European Medicines Agency (EMA), additional contraindications are reported for denosumab, namely severe, untreated hypocalcaemia and unhealed lesions from dental or oral surgery.[28 32]

Monthly zoledronate administration (4 mg) resulted in fewer SREs compared with placebo (33% zoledronate 4 mg vs 44% placebo; *P*=0.021) and reduced median time until first SRE (risk ratio [RR]: 0.672; *P*=0.012) in PC patients with BM (n=422).[23] The risk of SRE was reduced by 36% (*P*=0.002) in the zoledronate group vs the placebo group. Significant benefits of monthly zoledronate administration were further found for patients with other solid tumours (n=407). After 9 months of treatment, a significantly longer time until first SRE was found for zoledronate vs placebo (*P*=0.03). Risk of SREs was reduced by 30.7% in the zoledronate group vs the placebo group (*P*=0.003).

A phase 3 placebo-controlled RCT showed a statistically significant reduction in skeletal morbidity period rate in BC patients with BM (n=312) treated with monthly ibandronate (6 mg) vs placebo (skeletal morbidity period rate: 0.29; *P*=0.004).[24] This was equal to a risk reduction of 40%.

Monthly administration of denosumab (120 mg) was compared to monthly administration of zoledronate (4 mg) in cancer patients with BM in 3 RCTs.[28] In all 3 studies, denosumab reduced the risk of first and subsequent SREs:

- Study 1: 2,046 BC patients with BM; denosumab reduced SRE risk by 23% vs zoledronate (hazard ratio: 0.77; 95% CI: 0.66, 0.89; *P*=0.0012 for superiority)
- Study 2: 1,776 patients with solid tumours and BM or MM (excluding BC and PC); denosumab reduced SRE risk by 10% vs zoledronate (RR: 0.90; 95% CI: 0.77, 1.04; *P*=0.1447)
- Study 3: 1,901 PC patients BM; denosumab reduced SRE risk by 18% vs zoledronate (Hazard ratio: 0.82; 95% CI: 0.71, 0.94; *P*=0.0085 for superiority)

The adverse events (AEs) of zoledronate, ibandronate, and denosumab are similar, including nausea, diarrhoea, and weakness.[19 23 24 28] ONJ, a less frequent but potentially serious condition, is the most important AE associated with prolonged administration of BTAs.[19] Occurrence of ONJ was found to be

higher with monthly BTA administration compared with less frequent administration, and denosumab was found to be associated with higher ONJ rates compared with bisphosphonates.[19 33] For denosumab, fatal cases of hypocalcaemia have been reported.[34] Unlike BPs, denosumab does not accumulate in the bone, and its effect is reversible in the short term after treatment discontinuation, leading to a rise in bone markers and an increased risk of rebound-associated vertebral fractures (rebound effect of denosumab). Notably, studies in osteoporosis patients have shown a rapid rebound in bone turnover following the termination of treatment with denosumab. This rebound effect is also part of the discussion regarding the treatment with denosumab of cancer patients, potentially being at a higher risk for rebound fractures due to longer duration of treatment and higher dosages compared with osteoporosis patients.[19 29 35] Despite these safety concerns, denosumab was reported to be the BTA of choice in Switzerland, being used as initial therapy in 78.5% of patients.[18]

The administration frequency of every 3 to 4 weeks for zoledronate and ibandronate and every 4 weeks for denosumab according to the Swissmedic SmPC are based on the studies on hypercalcemia patients and coadministration with standard anticancer agents.[36 37] However, pharmacokinetic studies found terminal half-lives of BPs and denosumab to be longer.[38 39] Furthermore, recently published information showed evidence that after an initial phase of 3 to 6 months, these agents may also be administered every 3 months, which could help to avoid the incidence of AEs associated with monthly administration.[40 41] Currently, it is clinical practice in Switzerland that physicians initiate the admission of BTAs in cancer patients with BM as monthly therapy and might switch over to a less frequent dosing after 1 or 2 years.[18]

4.2 Alternative technologies

Treatment of BM in cancer patients often requires multidisciplinary therapy management. Beside BTAs, treatment may also include radiotherapy, radioisotope therapy, endocrine therapy, chemotherapy, biologically targeted therapy, immunotherapy, and surgical therapy.[6,18 19] As stated in Section 3.3, in some cases such as mHSPC where BTA treatment was not shown to be effective, only antitumour therapy is needed to treat BM.

Radiotherapy is most often the chosen treatment for localized bone pain caused by BM. Depending on the type of cancer, reported response rates go up to 85%, and complete pain relief is attained in half of these patients. Radioisotope therapy can be performed in cancer patients with more diffuse bone pain and to save normal tissue for unnecessary irradiation. However, many patients experience widespread pain or a recurrence of bone pain after radiotherapy.[19 42]

Endocrine therapy or chemotherapy are mainly applied to treat the primary cancer and, thus, depend on the cancer type, tumour growth rate, and general health of the patient. Consequently, both treatment procedures have an impact on the primary tumour and their derived BM.[43]

However, as resistance to systemic treatment of the underlying cancer disease can arise over time and enables the development of metastases, a change of therapy might be necessary.[19]

If bone fractures, paralysis, or severe pain occur, surgery can be performed to stabilize and reconstruct the broken part of the bone. For example, this might comprise injection of bone cement to the damaged bone as a minimally invasive surgery event.[44]

4.3 Regulatory status/provider

Zoledronate, ibandronate, and denosumab are available on the Swiss market and have been reimbursed by the compulsory health insurance since 2003 (Zometa®), 2006 (Bondronat®), and 2012 (Xgeva®). Table 1 presents an overview of the reimbursed indication per drug in Switzerland. Generic drugs are available for Zometa® (Status as of 3 May 2021).[23 24 28]

The BTAs zoledronate, ibandronate, and denosumab are approved by the EMA.[30-32] Information on reimbursement practices in other European countries was attained through searches on websites of the responsible authorities from selected European countries. An overview of the reimbursement status can be found in Table 2. The selection of the countries was made according to the countries listed as relevant for the external reference pricing in Switzerland named in Art. 34a KLV (Krankenpflege-Leistungsverordnung, Healthcare Benefits Ordinance).[45] No detailed information could be found on the reimbursement status specifically for the 3-monthly administration of the BTAs.

Table 1. Overview of indication and reimbursement of zoledronate, ibandronate, and denosumab in Switzerland

Active pharmaceutical ingredient	Brand name	Indication according to the Swissmedic-approved label[23 24 28]	Limitation (reimbursement) according to the specialty list[46]
Zoledronate	Zometa®	For the treatment of patients with BM from solid tumours and MM in combination with standard antineoplastic therapy Treatment of malignant hypercalcaemia, defined as albumin-corrected serum calcium >12.0 mg/dL (3.0 mmol/L)	-
Ibandronate	Bondronat®	Treatment of patients with BM in breast carcinoma	Treatment of patients with BM in breast carcinoma
Denosumab	Xgeva®	For the treatment of patients with BM from solid tumours in combination with standard antineoplastic therapy For the treatment of adults and adolescents with completed skeletal maturation with giant cell tumours of the bone that are either unresectable or for which resection would likely result in high morbidity	For the treatment of patients with BM from solid tumours in combination with standard antineoplastic therapy For the treatment of adults and adolescents with completed skeletal maturation with giant cell tumours of the bone that are either unresectable or for which resection would likely result in high morbidity
Key: BM – bone metastases; dL – decilitre; mg – milligram; MM – multiple myeloma.			

Additionally, information on the reimbursement status of these drugs in other Western countries outside of Europe was searched. In Australia, zoledronate, ibandronate, and denosumab are reimbursed with limitations: zoledronate is reimbursed for patients with MM and for patients with BM due to BC or castration-resistant PC; denosumab is reimbursed for the treatment of BM from BC or PC; and ibandronate only for BM due to BC.[47]

In the United States (US)[48] and Canada, reimbursement is not universally determined but depends on the health plan and state. For Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommends reimbursement for zoledronate and denosumab, whereas ibandronate is not available in Canada. However, the recommendation by CADTH is not binding.[49]

Table 2. Current national reimbursement status[a] of zoledronate, ibandronate, and denosumab in selected European countries

Country	M05BA08 / zoledronate	M05BX04 / ibandronate	M05BX04 / denosumab
Austria[50]	Reimbursed	Not reimbursed	Reimbursed
Belgium[51]	Reimbursed[b]	Reimbursed (mBC)	Reimbursed
Denmark[52]	Reimbursed	Reimbursed	Not reimbursed
Finland[53]	Partly reimbursed[c]	Partly reimbursed[c], fully reimbursed (mBC)	Reimbursed (mBC, mPC)
France[54]	Partly reimbursed[d]	Partly reimbursed[d] (mBC)	Reimbursed
Germany[55]	Reimbursed	Reimbursed	Reimbursed
The Netherlands[56]	Reimbursed	Reimbursed (mBC)	Reimbursed
Sweden[57]	Reimbursed	Reimbursed (mBC)	Not reimbursed
United Kingdom[58]	Reimbursed	Reimbursed (mBC)	Reimbursed[e]

[a] Reimbursement for the treatment of bone metastases; restrictions in brackets. State as of 17th of May 2021. [b] Patients receiving palliative care that no longer includes intravenous antineoplastic therapy. [c] Reimbursement rate 40%. [d] Reimbursement rate 65%. [e] Not for PC.

Key**:** ATC – anatomical-therapeutic-chemical classification; mBC – metastatic breast cancer; mPC – metastatic prostate cancer.

5 PICOS

Table 3 presents the PICOS scheme that specifies the parameters of patient populations, interventions, comparators, outcomes, and study designs to answer the research question.

Population

The relevant population for the present issue is defined as patients with cancer-related BM from solid tumours and patients with MM with bone involvement. No further patient characteristics were considered to determine eligibility.

Intervention

The investigated interventions are 3 types of BTAs (zoledronate, ibandronate, denosumab) that were considered separately. All medicinal products of these active ingredients that are licensed by Swissmedic for the indication of treating bone metastases are eligible. The relevant administration frequency is every 3 to 4 weeks for zoledronate and ibandronate and every 4 weeks for denosumab. Administration route and dosing intervals are those stated in the SmPC.[23 24 28]

Table 3. PICOS scheme

Population	• Patients with cancer-related BM from solid tumours • Patients with MM with bone involvement	
Intervention	• I 1: Monthly infusion (dosing interval per SmPC) of bisphosphonates (zoledronate or ibandronate) (all Swissmedic-licensed medicinal products)[a] • I 2: Monthly SC injection of denosumab (all Swissmedic-licensed medicinal products) (dosing interval per SmPC)	
Comparator	• C 1: 3-monthly infusion of bisphosphonates (zoledronate or ibandronate) (all Swissmedic-licensed medicinal products)[a] • C 2: 3-monthly SC injection of denosumab (all Swissmedic-licensed medicinal products)	
Outcomes (clinical)	Efficacy/effectiveness • **SREs (fractures, spinal cord compression, surgery/operation, radiotherapy)** • Quality of life • Bone pain • Bone-related markers/markers of bone turnover, including bone mineral density, N-/C-telopeptide-related markers	Safety • **AEs** (**any AE, serious AEs**, and specifically ONJ, renal AEs, and hypocalcaemia) • All-cause mortality
Outcomes (health economic)	• Costs (direct medical and non-medical), costs per clinical event, cost savings • ICER • QALYs and LYs • Utilities • Budget impact • Healthcare resource utilization	
Study designs/ types (clinical)	• RCTs and re-analysis of RCTs • HTA reports, SLRs, and meta-analyses from RCTs (for hand-searching of reference lists) • Non-RCTs (for long-term effects and/or if RCTs are unavailable)	
Study designs/ types (health economic)	• All economic evaluations, such as: o Budget impact o Cost benefit o Cost utility o Cost effectiveness o Cost comparison o Cost minimization	

Primary outcomes marked in bold.

Note: Assessment of the legal, social, ethical, and organisational aspects of all relevant outcomes and study designs/types will be considered to help answer the research questions.

[a] The aim of the report is not to compare the different bisphosphonates with each other but only different dosing regimens of each drug.

Key: AE – adverse event; BM – bone metastases; HTA – health technology assessment; ICER – incremental cost-effectiveness ratio; LY – life-year; MM – multiple myeloma; ONJ – osteonecrosis of the jaw; QALY – quality-adjusted life-year; RCT – randomized controlled trial; SC – subcutaneous; SLR – systematic literature review; SmPC – Summary of Medical Product Characteristics; SRE – skeletal-related event.

Comparator

The comparator for each intervention is the respective intervention with a longer dosing interval. The administration frequency is every 3 months. The BTAs are not compared with each other, only with the longer interval dosing, so zoledronate is compared only with zoledronate, ibandronate only with ibandronate, and denosumab only with denosumab.

Outcomes

For the domain including efficacy and effectiveness, the primary outcome is SREs. SREs are defined as fractures, spinal cord compression, surgery to the bone/operation, and radiotherapy. QoL, bone pain, and bone markers are secondary outcomes.

For the domain safety, the primary outcome is AEs including any AEs, and serious adverse events (SAEs). Secondary safety outcomes are ONJ, renal AEs, hypocalcaemia, and all-cause mortality.

For the domain including cost, cost-effectiveness, and budget impact, the following are of importance: costs (direct medical and non-medical), cost per clinical event, cost savings, incremental cost-effectiveness ratios (ICERs), quality-adjusted life-years (QALYs), life-years (LYs), utilities, budget impact, and healthcare resource utilization.

Study design

The eligible study designs for the domain including efficacy, effectiveness, and safety are RCTs and re-analyses of RCTs. HTA reports, systematic literature reviews (SLRs), and meta-analyses from RCTs were used to hand-search the reference list. Evidence from non-randomized controlled trials is also used to look at long-term effects.

Evidence from all economic evaluations is eligible for inclusion for the domain of costs, cost-effectiveness, and budget impact.

6 HTA key questions

For the evaluation of the technology, the following key questions covering central HTA domains, as designated by the EUnetHTA Core Model (clinical effectiveness; safety; costs; cost-effectiveness; budget impact; legal, social, ethical, and organisational aspects), are addressed:

1. Is the 3-monthly use of BTAs effective/efficacious compared to the monthly use?
2. Is the 3-monthly use of BTAs safe compared to the monthly use?
3. What are the costs of BTA use?

4. What is the budget impact of the 3-monthly use of BTAs vs monthly use?
5. How cost-effective is the less frequent use of BTAs?
6. Are there legal, social, or ethical issues related to the less frequent administration of BTAs?
7. Are there organisational issues related to the less frequent administration of BTAs?

6.1 Additional question(s)

NA

7 Effectiveness, efficacy, and safety

7.1 Methodology for effectiveness, efficacy, and safety

7.1.1 Databases and search strategy

The parameters described below were applied to all key questions listed in Section 6, except when noted otherwise.

To address the introduced research questions, relevant literature in line with the PICOS scheme had to be obtained. Relevant literature was identified through a systematic literature search and additional hand search (see Section 7.1.2). For the SLR, the following databases were searched via OVID:

- Medline
- Embase
- Evidence-Based Medicines Review (EBMR)
    - Cochrane Database of Systematic Reviews (CDSR)
    - Database of Abstracts of Reviews of Effects (DARE)
    - Health Technology Assessment (HTA)
    - National Health Service (NHS) Economic Evaluation Database (EED)
- Cochrane Central Register of Controlled Trials (CCTR)

The search strategies for each database were developed in consultation with an information specialist. A list of search terms based on the PICOS scheme was compiled to support the development of the search strings. The queries were developed as a combination of keywords and subject headings in line with the respective database. Complete search strategies and results are shown in Appendix 1. The search was limited to articles on the human use of the relevant drugs. The selection of relevant articles was done on the PIC level, so no search filters were applied for outcomes or study types. To test the search strategy, the search results were compared to a defined set of sentinel articles.

The first round of databases search was conducted on 27 May 2020 within the framework of the Scoping Report. To identify relevant studies published after 27 May 2020 and before the start of the model construction for the HTA report, a second round of database searches was performed on 18 January 2021.

All publications between 2000 and the day of search (18 January 2021) were included. The time horizon was chosen based on the fact that the active ingredients of interest achieved market authorization in 2001.[30 59] For conference abstracts, the search was limited to the years 2015 to 2021. We included only publications in English, German, and French and assumed that relevant articles would be published in these languages. For the screening of the database results, predefined inclusion and exclusion criteria were applied (Appendix 2). Duplicates across the different databases (n=1,463) were removed before screening.

All records were screened by 2 independent reviewers according to the inclusion and exclusion criteria. Differences in study selections were settled via consensus at each stage of the selection process. A third reviewer was consulted if no consensus could be reached. For the title and abstract screening, Distiller SR software was used. Reasons for exclusion were documented at the full-text review stage. A list of all these excluded hits with exclusion reasons can be found in Appendix 3. During the full-text screening phase, reference lists were cross-checked to find any other studies or systematic reviews that were not captured with the literature search.

In the case that a reference identified in one domain was also of relevance for another domain, this reference was forwarded. SLRs and meta-analyses were included to cross-check reference lists for further relevant publications.

If no full text of an included reference was available, published data from official websites (clinicaltrials.gov or the company website) were used if accessible.

7.1.2 Other sources

To check for any publications possibly missed by the database search, an additional hand search in Google Scholar and PubMed was conducted on 22 January 2021. The search terms were *zoledronate/ zoledronic acid*, *ibandronate/ibandronic acid*, and *denosumab*. Additionally, each of these terms was searched together with the term *bone metastases* or *de-escalation*. The time frame was set to 2000 to the date of search (22 January 2021).

Finally, the New York Academy of Medicine Grey Literature Report was consulted and checked for potentially relevant literature.

Conference abstracts were only searched for in the database search to make sure that the related full publications were included in the results. Therefore, Google Scholar was searched by hand for the

corresponding publications of the identified conference abstracts. If no full publication was available, the reason of exclusion “publication type” was noted.

7.1.3 Assessment of quality of evidence

For the critical appraisal, the methodological quality of the included studies was assessed and summarized using recognized standards for the systematic evaluation of scientific studies.

The quality analysis of the selected RCTs was performed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). The RoB 2 tool includes the following 5 domains for quality assessment of RCTs:

1) Bias arising from the randomization process
2) Bias due to deviations from intended interventions
3) Bias due to missing outcome data
4) Bias in measurement of the outcome
5) Bias in selection of the reported result

Domain-level judgements and overall judgements about the risk of bias were achieved by following the algorithm provided in the RoB 2 user guidelines. Possible risk of bias judgements in the RoB 2 tool are *low risk of bias*, *some concerns*, and *high risk of bias*.[60]

The quality of retrospective studies that were included in the meta-analysis for the purpose of sensitivity analyses was assessed using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool. This tool comprises a quality assessment based on the following 7 domains:

Pre-intervention:

1) Bias due to confounding
2) Bias in selection of participants into the study

At intervention:

3) Bias in classification of interventions

Post-intervention:

4) Bias due to deviations from intended interventions
5) Bias due to missing data
6) Bias in measurement of outcomes
7) Bias in selection of the reported results

Similar to the quality assessment based on the RoB 2 tool, domain-level judgements and overall judgements about the risk of bias were obtained by using the algorithm proposed in the ROBINS-I user

guidelines. Possible risk of bias judgements in the ROBINS-I tool are *low risk of bias*, *moderate risk of bias*, *serious risk of bias*, *critical risk of bias*, and *no information.*[61]

7.1.4 Methodology for data analyses for efficacy, effectiveness, and safety

Data extraction

Data were mainly derived from 1 publication for each study. However, for the RCTs assessing denosumab, 2 publications were available. If data on the outcomes of interest were not reported in the respective literature, study results were extracted from ClinicalTrials.gov. Additionally, if such data were not available on ClinicalTrials.gov, the prespecified outcomes were not considered in the analysis for the respective studies. As prespecified in the PICOS scheme (Table 3), the primary efficacy outcome of interest was the risk of SREs overall and SRE subtypes. QoL, bone pain, and bone markers were defined as secondary outcomes. The primary safety outcomes were AEs, including any AEs and SAEs. Secondary safety outcomes were risk of ONJ, renal AEs, hypocalcaemia, and all-cause mortality.

The outcome SRE risk was defined as the number of patients experiencing at least 1 SRE divided by the total number of patients. Since the study length varied across the identified literature, SRE data included in the analysis refer to the number of events during the study period. SRE subtypes reported in the studies were clinical or pathological fracture, spinal cord compression, radiation to bone, and surgery involving bone. Whilst the definition of fracture varied, the definition of SREs was assumed to be similar between studies. Two studies reported clinical fractures and were pooled with pathological fractures in this analysis.

Toxicity, in terms of AEs, SAEs, hypocalcaemia, ONJ, and renal AEs, was reported as events during the study period. The definition of renal AEs differed widely across the studies (Table 9 and Table 11). However, all available data on renal AEs were pooled in this analysis. Overall mortality data were presented in 5 RCTs, while 1 RCT assessing zoledronate[62] reported on-treatment deaths. All variables included were dichotomous. Although assessed in many studies for zoledronate, the outcome of pain score was not included in the analysis due to lack of standardization regarding the instrument and endpoint definition. Changes in levels of bone turnover markers including urinary or serum NTx and serum CTx were reported in 4 RCTs. However, definition of the outcome was inconsistent between the studies (e.g., regarding prespecified cut-off values and times). Thus, the data available on bone markers could not be pooled in this analysis. Finally, health-related quality of life (HRQoL) and global health status data were reported only in 1 study, presenting pooled data for zoledronate, denosumab, and an additional bisphosphonate (pamidronate). Assessment of pamidronate was outside of the scope of this report, so that pooled data for the 3 BTAs was not considered for the meta-analysis.

Meta-analysis

A meta-analysis was conducted in R (version 4.0.4) and R Studio Desktop (version 1.1.463) using a dmetar package to synthesize outcomes data. In the primary analysis, data from the studies assessing zoledronate and denosumab were pooled in accordance with the research question of this paper. In the meta-analysis, the Mantel-Haenszel method[63] was applied to provide pooled RRs with 95% confidence intervals (CIs). A continuity correction of 0.1 was applied for studies with zero cell frequencies solely when trial arms were very uneven in terms of their sample size.[64]

The treatment effect was estimated by using both a fixed effects (FE) model and a random effects (RE) model, when appropriate. An FE model is considered if only within-study variation exists, whereas an RE model additionally assumes between-study variation (Tau^2), which is more realistic. The main analysis was, thus, based on the RE model. However, when the number of studies is very small, there is uncertainty around the estimation of the Tau parameter in an RE model. Therefore, an FE model was used when only 2 studies were included in the meta-analysis. Additionally, the FE model was applied to all other analyses to assess the impact on the results from the main analysis. Furthermore, the results of RE meta-analyses provide prediction intervals giving a range in which the effects of future studies on the intervention of interest are expected to fall.[65]

The results of the meta-analyses are displayed by applying forest plots (Section 7.2.5). The results were considered statistically significant when the CI of the point estimate (RR) did not include the value "1".[66]

Heterogeneity

Between-study heterogeneity and inconsistency were determined by estimating Tau^2 and by employing the I^2 statistics and the Chi^2 test.[67] In the RE model, the Hartung-Knapp-Sidik-Jonkman (HKSJ) method was applied to estimate Tau^2 because it produces more robust estimates of between-study variances than the commonly applied DerSimonian-Laird method, especially in cases where the number of studies is small and where there is a substantial heterogeneity.[68] The RE model was applied only when more than 2 studies were included in the analysis, since the number of studies needs to be sufficient to enable the estimation of Tau^2. The HKSJ method usually leads to more conservative results, which is indicated by wider CIs.[68]

CIs for Tau and Tau^2 were obtained by applying the Q-profile method. Typically, very wide CIs for the parameter result from the low precision of the estimated between-study variance (Tau^2) in small samples (i.e., meta-analyses with few studies). Therefore, the Hartung-Knapp adjustment was applied for the RE model. This method uses quantiles of the *t* distribution rather than the standard normal distribution, as in the more conventional approach when computing a CI for the pooled average effect.[69]

For interpretation of I^2, the following "rule of thumb" was applied[67]:

- I^2=25%: Low heterogeneity
- I^2=50%: Moderate heterogeneity
- I^2=75%: High heterogeneity

Sensitivity analyses

Sensitivity analyses were conducted to evaluate the validity of the results from the main pooled analysis. Therefore, analyses were also performed assessing the effect of zoledronate and denosumab separately. To further enhance the statistical power of the pooled analysis, a sensitivity analysis including data from retrospective cohort studies for both BTAs was performed. Data from retrospective studies were only considered for this sensitivity analysis if these were found to be associated with a low or moderate risk of bias (see Section 7.2.4 and Appendix 6).

7.2 Results for effectiveness, efficacy, and safety

7.2.1 Evidence base pertaining to efficacy, effectiveness, and safety

The evaluation of the overall effectiveness of the technology encompasses its efficacy, its effectiveness, and its safety.

- Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (internal validity).
- Effectiveness is the extent to which a specific health technology, when applied in real-world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (external validity).
- Safety is a judgement of the harmful effects and their severity using the health technology. Relevant AEs are those that result in death, are life-threatening, require inpatient hospitalization, or cause prolongation of existing hospitalization (SAEs) and those that occur repetitively and most frequently (highest rate).

To identify evidence for efficacy, effectiveness, and safety, systematic literature searches in all the previously mentioned databases were performed. The results of the systematic literature searches that were performed are presented in Figure 1.

5,375 records were identified. Of those, 5,292 records were excluded based on their title and abstract, while 83 full texts were reviewed for eligibility. After assessment of the full texts, 64 records were excluded (see PRISMA flowchart for detailed exclusion details; Figure 1).

No further studies were identified through hand search or from reference lists of included SLRs (n=8).[40 41 70-74] An overview of the identified studies assessed in the SLRs is presented in Appendix 4.

During the screening, we also identified an ongoing RCT (SAKK96/12) that would fulfil our predefined inclusion criteria (Appendix 5). However, no preliminary results of the study were available at the time point of the second round of literature searches. Therefore, this study could not be considered in the meta-analysis underlying this HTA report. The SAKK96/12 trial is a noninferiority phase 3 trial led by the Swiss Group for Clinical Cancer Research, with recruitment sites in Switzerland, Austria, and Germany. Thus, the data will especially provide evidence for the utilization of BTAs in Switzerland and should be assessed after completion of the study. The estimated completion date of the trial is December 2022.[75]

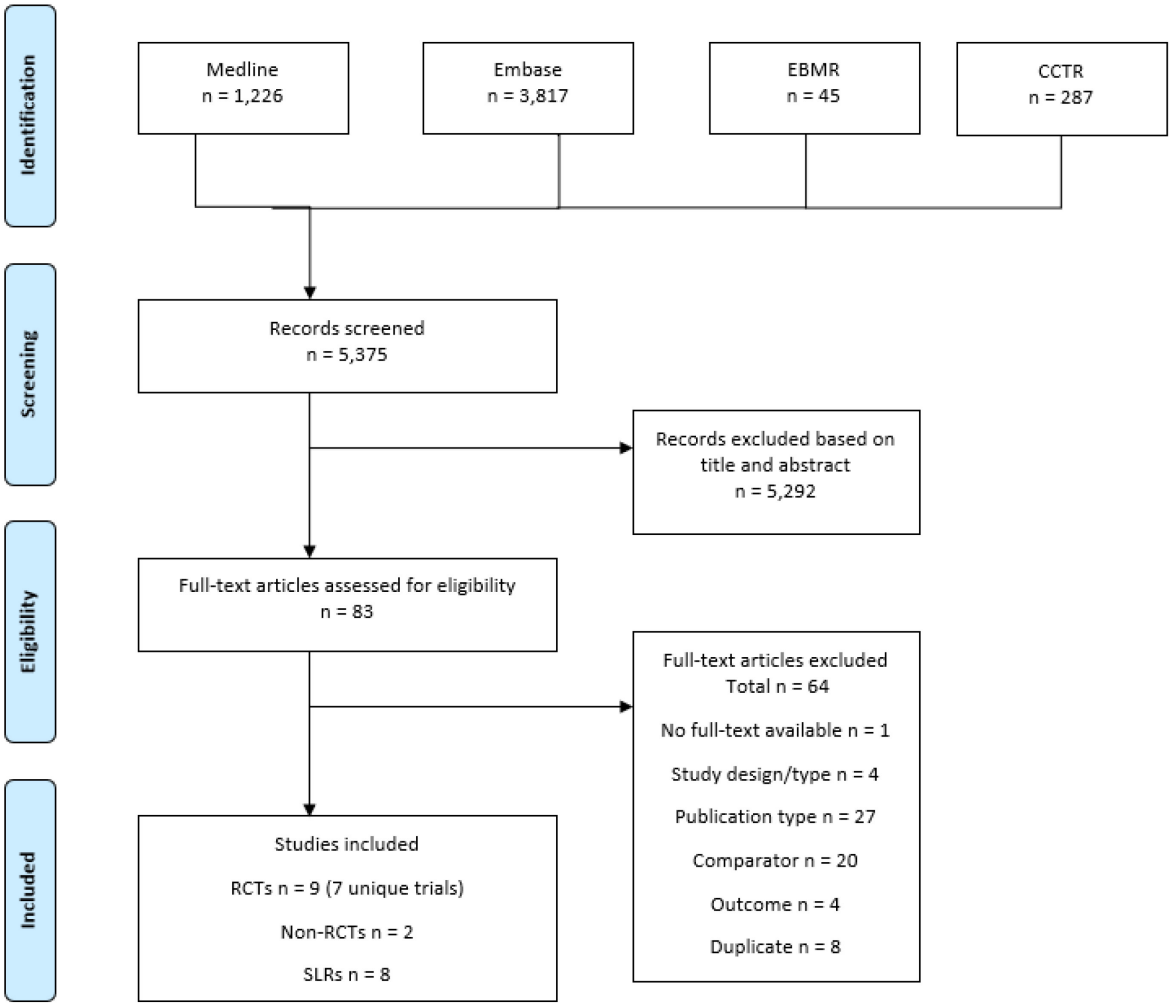
In total, we identified 7 unique RCTs (from 9 publications) and 2 retrospective studies reporting on clinical efficacy, effectiveness, and safety of administration of less frequent dosing with BTAs (every 3 months) compared to the standard dosing regimen (every month) (Table 4). Four RCTs and 1 non-RCT were found for zoledronate, 2 RCTs and 1 non-RCT were found for denosumab, and 1 was found RCT for both; these are summarised in Table 5 through Table 7. No trial was identified for ibandronate. 3 of the identified trials were noninferiority trials. The respective margins used in the studies to assess noninferiority are also reported in Table 5 through Table 7.

Table 4. Included studies identified by the systematic literature search

	Ibandronate	Zoledronate	Denosumab	Zoledronate and denosumab
Identified trials	No trials identified	4 RCTs[1 62 76 77] 1 non-RCT[78]	2 RCTs[2 79-81] 1 non-RCT[82]	1 RCT[83]
Key: RCT – randomized controlled trial.				

7.2.2 PRISMA flow diagram

Figure 1. PRISMA flowchart of the efficacy, effectiveness, and safety systematic literature search



Key: CCTR – Cochrane Central Register of Controlled Trials; EBMR – Evidence-Based Medicine Reviews; RCT – randomized controlled trial; SLR – systematic literature review.

7.2.3 Evidence table

The characteristics of the included RCTs and non-RCTs are presented in Table 5 (zoledronate), Table 6 (denosumab), and Table 7 (zoledronate and denosumab).

Table 5. Studies with zoledronate: study characteristics

	Trial/ reference	Study design	Population/N	Intervention	Comparator	Efficacy/ effectiveness outcomes	Safety outcomes	RoB
RCTs	**Hortobagyi et al. (2017)[62]** OPTIMIZE-2 *NCT00320710*	• Phase 3, randomized (1:1), double-blind, multicentre, national, noninferiority[a] • 102 centres in the US • 1 year of study treatment • 1 year of follow-up	• mBC • Pretreated with BPs n=416	Zoledronate (IV) every 4 weeks n=200	Zoledronate (IV) every 12 weeks n=203 Placebo n=13	• SREs • Pain (BPI, analgesic score) • Bone markers • SMRs	Incidence of AEs	Some concerns
	Himelstein et al. (2017)[77] CALGB 70604 *NCT00869206*	• Phase 3, randomized (1:1), open-label, multicentre, national, noninferiority[b] • 269 sites in the US • 2 years of study treatment • 2 years of follow-up	• mBC, mPC, MM with bone involvement • Pretreated with BPs n=1,822	Zoledronate (IV) every 4 weeks n=911	Zoledronate (IV) every 12 weeks n=911	• SREs • Pain (BPI) • ECOG PS • SMRs • Bone markers	Incidence of AEs, especially ONJ and renal dysfunction	Low
	Amadori et al. (2013)[1] ZOOM *NCT00375427*	• Phase 3, randomized (1:1), open-label, multicentre, national, noninferiority[c] • Study sites in Italy • 1 year of study treatment • 1 year of follow-up	• mBC • Pretreated with zoledronate n=430	Zoledronate (IV) every 4 weeks n=216	Zoledronate (IV) every 12 weeks n=209	• SMRs • SREs • Pain (BPI, VRS, analgesic score) • ECOG PS	Incidence of AEs, especially ONJ and renal dysfunction	Some concerns
	Novartis (2012)[76]	• Phase 1, randomized (1:1), open-label, multicentre, national	• mBC, MM with bone involvement	Zoledronate (IV) every 4 weeks	Zoledronate (IV) every 12 weeks n=9	• SREs • PK parameters	Incidence of AEs	Some concerns

	Trial/ reference	Study design	Population/N	Intervention	Comparator	Efficacy/ effectiveness outcomes	Safety outcomes	RoB
	NCT00424983	• 7 study sites in the US • 1 year of study treatment	• Pretreated with zoledronate n=18	n=9				
Non-RCT	**Tam et al. (2020)[78]**	• Single-centre, retrospective cohort analysis • 1 centre in the US • 1 year of follow-up	• NSCLC/SCLC with at least 1 BM n=80	Zoledronate (IV) every 4 weeks n=46	Zoledronate (IV) every 12 weeks n=34	• SREs • Time to first SRE • OS • Pain (NPRS score)	Incidence of ONJ, kidney dysfunction, hypocalcaemia	Moderate

[a] Noninferiority margin: 10% in relation to absolute difference in SRE.

[b] Noninferiority margin: 7% in relation to absolute difference in SRE.

[c] Noninferiority margin: 19% in relation to SMR.

Key: AE – adverse event; BM – bone metastases; BP – bisphosphonate; BPI – Brief Pain Inventory; ECOG – Eastern Cooperative Oncology Group; IV – intravenous; mBC – metastatic breast cancer; MM – multiple myeloma; mPC – metastatic prostate cancer; NPRS – Numeric Pain Rating Scale; NSCLC – nonsmall cell lung cancer; ONJ – osteonecrosis of the jaw; OS – overall survival; PK – pharmacokinetics; PS – performance status; RCT – randomized controlled trial; RoB – risk of bias; SCLC – small cell lung cancer; SMR – skeletal morbidity rate; SRE – skeletal-related event; US – United States; VRS – visual rating scale.

Table 6. Studies with denosumab: study characteristics

	Trial/ reference	Study design	Population/N	Intervention	Comparator	Efficacy/ effectiveness outcomes	Safety outcomes	RoB
RCTs	**Lipton et al. (2007 and 2008)[2 81]** *NCT00091832*	• Phase 2, randomized (1:1:1:1:1:1:1), multidose, multicentre, international • Blinding of assigned dose and frequency for patients receiving denosumab • 56 centres in North America, Australia, and Europe	• mBC • Treatment-naive n=255	Denosumab (SC) every 4 weeks (30 mg [n=42], 120 mg [n=42], or **180 mg [n=43]**)[a]	Denosumab (SC) every 12 weeks (60 mg [n=42] or **180 mg [n=43]**)[a] Bisphosphonates (zoledronate, ibandronate or pamidronate; IV) every 4 weeks	• SREs • Bone markers	Incidence of AEs, especially hypercalcaemia	Some concerns

	Trial/ reference	Study design	Population/N	Intervention	Comparator	Efficacy/ effectiveness outcomes	Safety outcomes	RoB
		• 24 weeks of study treatment • 32 weeks of follow-up			n=43			
	Fizazi et al. (2009 and 2013)[79 80] *NCT00104650*	• Phase 2, randomized (1:1:1), open-label, multicentre, international • 26 centres in North America and Europe • 25 weeks of study treatment • 32 weeks of follow-up	• mBC, mPC, MM with BM • Pretreated with BPs n=111	Denosumab (SC) 180 mg every 4 weeks (n=38)	Denosumab (SC) 180 mg every 12 weeks (n=36) Bisphosphonates (zoledronate, pamidronate; IV) every 4 weeks n=37	• SREs • Bone markers	Incidence of AEs, especially hypercalcaemia	Some concerns
Non-RCT	**Abousaud et al. (2020)**[82]	• Retrospective cohort study • 1 centre in the US • Minimum follow-up of 11 months	• BM from solid cancers n=555	Denosumab (SC) 120 mg, dosing interval of **<5 weeks (short interval)**[a] **n=241**	Denosumab (SC) 120 mg, dosing interval of **≥12 weeks (long interval)**[a] **n=46** Denosumab (SC) 120 mg, dosing interval of 5–11 weeks (medium interval) n=145	• Time to first SRE • OS	Hospitalization, hypocalcaemia, ONJ	Moderate

[a] Intervention/comparator considered in this report in bold.
Key: AE – adverse event; BM – bone metastases; BP – bisphosphonate; IV – intravenous; mBC – metastatic breast cancer; MM – multiple myeloma; mPC – metastatic prostate cancer; ONJ – osteonecrosis of the jaw; OS – overall survival; RCT – randomized controlled trial; RoB – risk of bias; SC – subcutaneous; SRE – skeletal-related event.

Table 7. RCT with zoledronate and denosumab: study characteristics

	Trial/reference	Study design	Population/N	Intervention	Comparator	Efficacy/ effectiveness outcomes	Safety outcomes	RoB
RCT	**Clemons et al. (2021)[83]** *REaCT-BTA* *NCT02721433*	• Pragmatic, randomized (1:1), open-label, noninferiority[a] • 5 centres in Canada • 1 year of study treatment • 1 year of follow-up	• BM from BC or CRPC n=263	Zoledronate or denosumab or pamidronate + calcium + vitamin D every 4 weeks n=133	Zoledronate or denosumab or pamidronate + calcium + vitamin D every 12 weeks n=130	• HRQoL score • Pain • Global health status • SSEs	Toxicity	Some concerns

[a] Noninferiority margin: 5 points on the C30 physical subdomain.

Key: BC – breast cancer; BM – bone metastases; CRPC – castration-resistant prostate cancer; HRQoL – health-related quality of life; RCT – randomized controlled trial; RoB – risk of bias; SSE – symptomatic skeletal event.

7.2.4 Findings from the literature search regarding efficacy, effectiveness, and safety

7.2.4.1 Findings for de-escalated zoledronate

Efficacy

Of the 4 RCTs investigating the de-escalation of zoledronate, 3 were phase 3 studies, with 416 (Hortobagyi 2017, OPTIMIZE-2),[62] 430 (Amadori 2013, ZOOM),[1] and 1,822 patients (Himelstein 2017, CALGB 70604)[77], while 1 trial (Novartis 2012, NCT00424983)[76] was a phase 1 study with 18 patients. In total, 2,642 patients were treated with zoledronate in all identified RCTs. In all 4 studies, patients were randomly assigned (1:1) to either monthly or 3-monthly treatment with zoledronate. Hortobagyi 2017 was the only double-blinded study; the other trials were open-label. National studies were performed in multiple centres in the US (Hortobagyi 2017, Himelstein 2017, or Novartis 2012) or in Italy (Amadori 2013). Patients with mBC were included in all studies. Patients with BM due to MM were additionally included in the Novartis trial and patients with mPC in the Himelstein trial. All patients were previously treated with BPs before entering the study. Thus, most evidence for zoledronate is in pre-treated BC patients with BM.

All 4 studies compared the risk of SREs, defined as clinical or pathological fracture, spinal cord compression, surgery involving bone, and radiation to bone. For the Hortobagyi 2017 trial, risk of spinal cord compression and surgery involving bone was not reported separately from the combined SRE endpoint. No clear distinction between asymptomatic and symptomatic fractures was made in 3 (Hortobagyi 2017, Novartis 2012, Amadori 2013)[1 62 76] of 4 studies. 3 studies (Amadori 2013, Hortobagyi 2017, Himelstein 2017) analysed changes in pain using the Brief Pain Inventory (BPI) and the 6-point Verbal Rating Scale (VRS) pain score. 2 studies (Amadori 2013, Himelstein 2017) compared bone turnover by analysis of bone markers as surrogate endpoints.

Amadori et al. (2013) found no significant difference in skeletal morbidity rate (SMR) (SREs per patient per year) between the 3-monthly and the monthly administration of zoledronate (SMR 3-monthly: 0.26 [95% CI: 0.15, 0.37]; SMR monthly: 0.22 [95% CI: 0.14, 0.29]; between-group difference of 0.04 [1-sided 97.5% CI: 0.17]). The noninferiority margin was 19%.

Both Hortobagyi et al. (2017) and Himelstein et al. (2017) assessed the proportion of patients with at least 1 SRE (SRE rate) as the primary endpoint and concluded noninferiority of 3-monthly administration compared with monthly administration of zoledronate with predefined noninferiority margins of 10% and 7%, respectively. Hortobagyi et al. (2017) found a proportional difference in the SRE rate of −1.2% (1-sided 97.5% CI: −9.8%, noninferiority; P=0.02) and Himelstein et al. (2017) of −0.3% (1-sided 95% CI: −4% to ∞, noninferiority; P<0.001).

Novartis (2012) assessed the SRE rate as secondary outcome. 2 patients (22.2%) in the 3-monthly administration group and 1 patient (11.1%) in the monthly administration group experienced at least 1 SRE.

A recently completed RCT investigating the de-escalation of the BTAs zoledronate, denosumab, and pamidronate (Clemons 2021, REaCT-BTA)[83] was identified during the database searches. This pragmatic randomized (1:1), open-label, noninferiority trial was conducted at 5 Canadian centres and included 263 patients with BM from BC or castration-resistant prostate cancer (CRPC). The primary outcome was the change in patient HRQoL scores (EORTC-QLQ-C30 physical subdomain). The efficacy outcomes assessed were symptomatic skeletal events (SSEs), defined as pathological fracture, spinal cord compression, surgery to bone, radiotherapy to bone, and mean time to SSEs and changes in pain based on the Edmonton Symptom Assessment System (ESAS) pain score. Although the inclusion criteria for the meta-analysis were theoretically fulfilled, data from the REaCT-BTA trial could not be considered since Clemons at al. (2021)[83] reported only pooled data for zoledronate, denosumab, and pamidronate. Pooled data could not be included in the sensitivity analyses because assessment of the efficacy, effectiveness, and safety of pamidronate is not part of this HTA report.

Effectiveness

A single-centre, retrospective cohort analysis of monthly vs 3-monthly administration of zoledronate[78] was identified during the updated databases search. This analysis represents a real-world cohort of 80 patients with metastatic nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC) with at least 1 BM treated at 1 centre in the US between 1 January 2012 and 31 December 2018. 3-monthly administration of zoledronate to treat BM in NSCLC and SCLC was adopted as the new standard of care by clinicians of the institution after results of the Himelstein 2017 trial[77] were available. The cohort analysis assessed the risk of SREs, defined as clinical fracture, spinal cord compression, bone surgery, and radiation to bone within 1 year of zoledronate initiation, as well as time to first SRE and changes in pain based on the Numeric Pain Rating Scale (NPRS). Incidence of SREs at 1 year did not differ significantly between the 2 groups (3-monthly: 23.5% vs monthly: 23.9%; 95% CI: −0.184, 0.192; *P*=0.968).

As stated in Section 7.1.4, efficacy and effectiveness data on bone pain, bone markers, and QoL were not included in the meta-analysis due to limited data available and inconsistencies in measurement and definitions of outcomes. However, results are reported in Table 8.

Table 8. Efficacy, effectiveness, and quality of life data on bone pain, bone markers, and quality of life (zoledronate)

Outcome	Study	Definition	Time point of assessment	Results	
				3-monthly administration	Monthly administration
Bone pain	Amadori et al. 2013	Median 6-point VRS[a]	At rest		
			Baseline	1 (79%)	1 (86%)
			3 months	2 (84%)	2 (89%)
			6 months	2 (84%)	1 (86%)
			9 months	1 (76%)	1 (88%)
			End of study	2 (78%)	1 (85%)
			At movement		
			Baseline	2 (76%)	2 (79%)
			3 months	2 (73%)	2 (79%)
			6 months	2 (73%)	2 (79%)
			9 months	2 (68%)	2 (72%)
			End of study	3 (68%)	2 (72%)
	Himelstein et al. 2017	BPI score (estimated time slopes from longitudinal models. These represent the estimated score change that is associated with a 1-unit (in this case 1 visit) increase in time[b]			
		Worst pain, mean (SD)	Baseline	3.40 (3.19)	3.41 (3.10)
		Least pain, mean (SD)	Baseline	1.62 (2.25)	1.54 (1.95)
		Average pain, mean (SD)	Baseline	2.65 (2.56)	2.57 (2.36)
		Current pain, mean (SD)	Baseline	1.94 (2.48)	1.92 (2.43)
		Composite pain, mean (SD)	Baseline	2.41 (2.39)	2.36 (2.23)
		Relief from pain, mean (SD)	Baseline	5.47 (3.78)	5.63 (3.65)

Outcome	Study	Definition	Time point of assessment	Results	
				3-monthly administration	Monthly administration
		Interference, mean (SD)	Baseline	2.07 (2.53)	2.17 (2.54)
		Worst pain	1-unit increase	0.022	0.021
		Least pain	1-unit increase	0.007	0.013
		Average pain	1-unit increase	0.008	0.011
		Current pain	1-unit increase	0.016	0.018
		Composite pain	1-unit increase	0.021	0.022
		Relief from pain	1-unit increase	0.009	0.016
		Interference	1-unit increase	0.023	0.019
	Hortobagyi et al. 2017	Change from baseline in mean composite BPI score, mean (SD)[c]	Baseline	29.7 (6.3)	29.5 (6.2)
			52 weeks	0.31 (2.099)	0.24 (1.976)
	Tam et al. 2020	NPRS score, mean (SD)[b]	3 months	1.38 (2.22)	1.31 (2.46)
			6 months	1.04 (2.10)	1.33 (2.44)
			9 months	1.94 (2.95)	1.89 (3.18)
			12 months	1.33 (2)	1.25 (2.5)
		Change from baseline in NPRS, mean (SD)[b]	3 months	−0.59 (2.95)	0.48 (2.80)
			6 months	−0.32 (2.34)	−1.06 (3.63)
			9 months	0.29 (4.12)	−0.33 (2.87)
			12 months	−1.33 (3.67)	−1.57 (3.05)
	Clemons et al. 2020	ESAS pain score, mean (SD)[b] (zoledronate, denosumab, and pamidronate pooled)		3.2 (2.4)	2.6 (1.9)
Bone	Amadori et	Median percentage change from	6 months	12.2%	−2.3%

Outcome	Study	Definition	Time point of assessment	Results	
				3-monthly administration	Monthly administration
markers	al. 2013	baseline in N-terminal telopeptide concentration	9 months	10.6%	−2.2%
			12 months	12.2%	0.0%
	Himelstein et al. 2017	Mean C-telopeptide levels	Observed C-telopeptide levels were higher at each time point among patients receiving zoledronate every 12 weeks Please refer to figure 3 of Himelstein et al. 2017 In a longitudinal C-terminal telopeptide model, C-terminal telopeptide levels were found to be significantly lower in the monthly than in the 3-monthly administration group		
Quality of life	Clemons et al. 2020	EORTC-QLQ-C30, mean change in physical subdomain score from baseline (SD)[b] (zoledronate only)	Week 48	0.0 (18.2)	−3.7 (18.5)
		Global quality of life, change from baseline to post-baseline (zoledronate, denosumab, and pamidronate pooled)[d]	Across timepoints	−2.7	−7.4

[a] Percentages in parentheses are number of patients with score <4/number of patients with data available. [b] Differences were not statistically significant. [c] Data retrieved from ClinicalTrials.gov (NCT00320710). [d] Difference was statistically significant (*P*=0.006)

Key: BPI – Brief Pain Inventory; CI – confidence interval; ESAS – Edmonton Symptom Assessment System; NPRS – Numeric Pain Rating Scale; SD – standard deviation; VRS – Verbal Rating Scale.

Safety and mortality

Serious and non-serious AEs were reported in the 4 included RCTs (Hortobagyi 2017[62], Amadori 2013[1], Himelstein 2017[77], and Novartis 2012[76]) but not in the retrospective study[78]. Commonly occurring toxicity from long-term treatment with BTAs in terms of renal adverse events (RAEs) and ONJ was examined in all 5 studies, while hypocalcaemia was assessed only in 2 RCTs (Himelstein 2017[77] and Novartis 2012[76]) and in the retrospective study[78]. However, the definition of RAEs differed between the studies (Table 9). Overall mortality was reported for 3 RCTs (Amadori 2013[1], Himelstein 2017[77], Novartis 2012[76]), while 1 RCT (Hortobagyi 2017[62]) presented on-treatment deaths.

Table 9. Definition of RAEs in the studies assessing de-escalation of zoledronate

Study	Definition RAEs
Amadori et al. (2013)[1]	• Renal failure
Himelstein et al. (2017)[77]	• Increased creatinine level vs baseline level • Renal and urinary disorders (e.g., renal failure, urinary incontinence, urogenital disorders)
Hortobagyi et al. (2017)[62]	• Investigations (blood creatinine increased, creatinine renal clearance decreased, blood urea increased, creatinine renal clearance abnormal, GFR decreased) • Renal and urinary disorders (renal failure, renal failure acute, azotaemia, renal impairment)
Novartis (2012)[76]	• Renal and urinary disorders (serious/non-serious) • Renal function deterioration (defined by serum creatinine level)
Tam et al. (2020)[78]	• Grade 2 kidney dysfunction (CTCAE v5.0)
Key: CTCAE – Common Terminology Criteria for Adverse Events; GFR – glomerular filtration rate; RAE – renal adverse event.	

Limitations

The quality of evidence of the zoledronate studies is affected by the following limitations. The Novartis 2012[76] trial is a phase 1 study with only 9 patients in each treatment arm, resulting in low statistical study power. The treatment duration varied between the phase 3 trials, although study treatment duration was at least 1 year for all of them. Importantly, the Himelstein 2017[77] and Amadori 2103[1] trials are open-label studies with differences in frequency of clinic visits that were mainly determined by the dosing schedule. This could introduce a detection bias for AEs in the monthly administration group, but patient-reported outcomes in the 3-monthly administration group like the pain assessment could also be biased. In the cohort analysis, a possibility of selection bias arises due to its retrospective character. Although the 3-monthly administration of zoledronate was defined as standard of care at the study centre after completion of the Himelstein 2017 trial, information on the real intervention interval for each patient is lacking. Thus, individual selection into the monthly dosing scheme due to, for example, clinical reasons cannot be excluded. However, since the study shows a moderate overall risk of bias (Appendix 6), the

data were included in the sensitivity analysis of the meta-analysis. The full RoB assessment for both the RCTs and the non-RCT can be found in Appendix 6.

3 of the 4 included trials investigating zoledronate are noninferiority trials. Amadori 2013 reports the noninferiority margin for SMR (SREs per patient per year) whilst Himelstein 2017 and Hortobagyi 2017 report their margin for SRE rate (number of patients with at least 1 SRE). Neither Amadori 2013 nor Hortobyagi 2017 justify their chosen margin. Himelstein 2017 justifies the margin by reference to 4 other studies investigating the treatment effect of zoledronate vs placebo in different cancer types. As the predefined margins differ and there seems to be no clinical consensus around a noninferiority margin for the outcome of interest, this has implications for the interpretation of the results of the meta-analysis regarding the noninferiority of 3-monthly vs monthly BTA administration.

Most data were for patients with mBC and none of the trials included patients from Switzerland. Thus, evidence of the effectiveness of 3-monthly dosing vs monthly dosing with zoledronate for Swiss patients with PC, LC, or MM with bone involvement is limited.

7.2.4.2 Findings for de-escalated denosumab

Efficacy

We identified 2 phase 2 studies investigating the treatment effects of different denosumab doses with 255 (Lipton)[2 81] and 111 patients (Fizazi)[79 80]. The studies were not designed as noninferiority studies and compared denosumab to intravenous bisphosphonates. Both multidose studies compared treatment arms of monthly dosing of 180 mg denosumab (Lipton: 43 patients; Fizazi: 38 patients) and 3-monthly dosing of 180mg denosumab (Lipton: 43 patients; Fizazi: 36 patients). It should be noted that denosumab is licensed in Switzerland as monthly therapy with 120 mg. As the identified studies did not provide a comparison of monthly treatment with 120 mg vs 3-monthly treatment with 120 mg denosumab, the comparison of the 180 mg denosumab dosing schedules was considered. Patients of both studies were randomly assigned to one of the treatment arms, although information on whether the allocation was concealed is missing. While patients in the Lipton trial were blinded regarding their treatment with denosumab, the Fizazi trial was an open-label trial. Both studies were performed internationally, including study centres in North America and Europe. Only patients with mBC were included in Lipton, while Fizazi additionally included patients with mPC and MM with bone involvement. Moreover, patients in Lipton were treatment-naïve, while the patients in the Fizazi trial were pre-treated with BPs.

Regarding clinical outcomes, both studies analysed the risk of SREs as a secondary outcome. SREs were defined as ≥1 of the following: pathological bone fracture, spinal cord compression, surgery, or

radiation therapy to bone (including the use of radioisotopes). No differentiation between asymptomatic and symptomatic fractures was made. Additionally, both studies investigated bone turnover by analysis of the bone markers NTx and CTx as surrogate endpoints.

Fizazi et al. (2009) reported 4 patients (11%) in the 3-monthly group vs 2 patients (5%) in the monthly administration group with at least 1 SRE by the end of the study. Results on incidence of SREs for Lipton et al. (2007, 2008) were reported on ClinicalTrials.gov[84]. 4 patients (9%) in the 3-monthly group and 6 patients (14%) in the monthly administration group had experienced at least 1 SRE at study end.

As stated in Section 7.2.4.1, a recently conducted RCT (Clemons et al. 2020) reported pooled efficacy and HRQoL results for zoledronate, denosumab, and pamidronate. Only the mean change in the physical subdomain score of the EORTC-QLQ-C30 from baseline was reported separately for denosumab. HRQoL and bone marker results from the studies are presented in Table 10. Therefore, pooling the data in a meta-analysis was not possible due to limited data available and varying definitions of outcomes.

Table 10. Efficacy and quality of life data on skeletal morbidity rate, bone pain, bone markers, and quality of life (denosumab)

Outcome	Study	Definition	Time point of assessment	Results	
				3-monthly administration	Monthly administration
Bone markers	Fizazi et al. 2009 and 2013 (data from ClinicalTrials.gov)	Number of patients with uNTx (corrected by creatinine) <50 Nmol/mmol	Week 13	21/33	28/36
			Week 25	21/33	23/36
		Percentage change of uNTx from baseline, mean (SD)	Week 25	−69.09 (29.97)	−41.68 (118.32)
		Percentage change of sCTx from baseline, mean (SD)	Week 25	−76.74 (19.74)	−68.39 (36.15)
	Lipton et al. (data from ClinicalTrials.gov)	Percent change from baseline in uNTX/Cr, mean (SD)	Week 13	−18.46 (125.86)	−57.36 (41.46)
			Week 25	−39.96 (65.85)	−59.41 (43.31)
		Number of participants achieving 65% or more reduction in uNTx from baseline	Week 13	21/42	24/43
			Week 25	15/42	25/43
		Percentage change of sCTx from baseline, mean (SD)	Week 13	−78.13 (16.66)	−81.79 (13.29)
			Week 25	−78.31 (14.00)	−80.07 (22.26)
Quality of life	Clemons et al. 2020	EORTC-QLQ-C30, mean change in physical subdomain score from baseline (SD)[a] (denosumab only)	Week 48	−4.0 (26.1)	−5.8 (23.9)

[a] Differences were not statistically significant.

Key: SD – standard deviation; sCTX – serum C-terminal telopeptide; uNTX – urinary N-telopeptide.

Effectiveness

A retrospective cohort study assessing the clinical effectiveness and safety of different dosing intervals of denosumab at 1 centre in the US[82] was identified during the updated database searches. The study represents a real-word population of 432 patients with solid cancers (BC, PC, and LC) and BM who were treated with 120 mg denosumab with a dosing interval of either <5 weeks (short interval), 5 to 11 weeks (medium interval), or ≥12 weeks (long interval) between 1 November 2010 and 27 July 2018. The medium-interval dosing was assessed since this administration scenario is also observed in clinical practice. However, for the purpose of this report, only the data for the short-interval and the long-interval subgroups were compared, as they best fit to the research question of the HTA. In terms of effectiveness outcomes, the risk of SREs, defined as pathological fracture, spinal cord compression, surgery, and radiation, and the time to first SRE, was assessed. The primary outcome of the study was time to first SRE while on denosumab. In total, 18 SREs were reported for the 3-monthly administration group (n=46) and 152 SREs for the monthly administration group (n=241).

Safety and mortality

Serious and non-serious AEs were reported in the 2 included RCTs (Lipton[2 81] and Fizazi[79 80]) but not in the retrospective study.[82] Commonly occurring toxicities from long-term treatment with BTAs in terms of hypocalcaemia, RAEs, and ONJ were examined in both RCTs (Lipton[2 81] and Fizazi[79 80]), while the retrospective study assessed only hypocalcaemia and ONJ. However, definition of RAEs differed between the studies (Table 11). Overall mortality was reported for both RCTs.

Table 11. Definition of RAEs in the studies assessing de-escalation of denosumab

Study	Definition RAEs
Fizazi et al., 2009 and 2013[79 80]	Renal and urinary disorders (dysuria, haematuria, kidney enlargement, renal failure, renal failure acute, renal tubular necrosis, urinary retention, pollakiuria)
Lipton et al., 2007 and 2008[2 81]	Renal and urinary disorders (renal failure acute, urinary retention)
Key: RAE – renal adverse event.	

Limitations

Several factors limit the quality of evidence due to the heterogeneity of the denosumab studies. In the Lipton trial[2 81], the focus was on the dosing and frequency of denosumab administration, explaining the multiple study arms. In the Fizazi trial[79 80], the focus was on the comparison of denosumab vs BPs and thus results of both denosumab arms were compared to those of the zoledronate. Consequently, the number of patients comparing monthly dosing with 3-monthly dosing of denosumab is quite low, resulting in low statistical power, especially regarding rare events, such as severe AEs. Additionally,

patients differed between both studies regarding pre-treatment with BPs. Moreover, the open-label nature of Fizazi trial may lead to reporting bias. In addition, the findings from the retrospective cohort study are likely to be biased due to selection of patients into treatment groups, as the allocation was not random and reasons for the allocation were not provided. However, the overall risk of bias for the study was assessed and found to be moderate (Appendix 6). Therefore, the data were included in the sensitivity analysis of the meta-analysis. The full RoB assessment for both the RCTs and the non-RCT can be found in Appendix 6.

7.2.5 Findings from the meta-analysis regarding efficacy, effectiveness, and safety

In the following section, the key HTA questions regarding efficacy/effectiveness and safety of 3-monthly administration of BTAs compared to monthly administration are answered based on the results from the meta-analysis.

Question 1: Is the 3-monthly use of BTAs effective/efficacious compared to monthly use?

Skeletal-related events (overall)

SREs, defined as clinical or pathologic fracture, spinal cord compression, radiation to bone, and surgery involving bone, were reported in 4 RCTs[1 62 76 77] assessing the 3-monthly vs monthly use of zoledronate. Data on the overall risk of SREs (number of patients experiencing at least 1 SRE divided by the total number of patients) for zoledronate from all 4 studies (n=2,668) were included in the meta-analysis. For denosumab, 2 studies (Fizazi et al., 2009 and 2013[79 80]; Lipton et al., 2007 and 2008[2 81]) reporting on the risk of SREs in patients receiving 3-monthly vs monthly administration were included (n=160).

The absolute risk of SREs ranged from 5% to 29% for monthly and 9% to 28% for 3-monthly administration (Table 12).

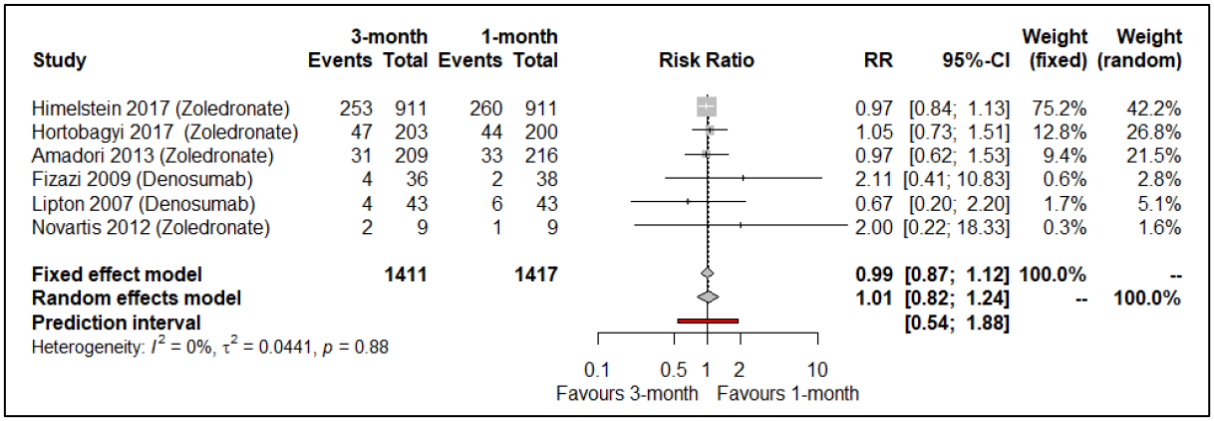
Table 12. Absolute risk of SREs in the studies included in the meta-analysis

Study	Absolute risk	
	3-monthly	Monthly
Himelstein et al. 2017[76]	28%	29%
Hortobagyi et al. 2017[62]	23%	22%
Amadori et al. 2013[1]	15%	15%
Fizazi et al. 2009[79 80]	11%	5%
Lipton et al. 2007[2 81]	9%	14%
Novartis 2012[76]	22%	11%

Overall, the results for the meta-analysis of the 3-monthly and the monthly dosing interval of BTAs regarding the risk of SREs indicate no statistically significant difference (RE: RR: 1.01; 95% CI: 0.82, 1.24; FE: RR: 0.99; 95% CI: 0.87, 1.12; prediction interval: 0.54, 1.88) (Figure 2). The CI of the RE analysis suggests that 3-monthly administration of BTAs in cancer patients with bone involvement instead of the monthly administration regimen may increase the risk of SREs by up to 24% or may reduce it by up to 18%. Between-study heterogeneity was low (I^2=0%). Wide CIs of the effect estimates in Fizazi (0.41, 10.83), Lipton (0.20, 2.20), and Novartis (0.22, 18.33) are caused by small sample sizes and the fact that the events of interest generally occur rarely.

As described in 7.2.4.1, 3 of the included analysed studies are noninferiority trials. Of these 3, Himelstein and Hortobagyi specified a noninferiority margin for SREs. Since the reported margin in these publications are based on absolute treatment effects, the margins need to be converted to relative treatment effects to compare the findings of the presented meta-analysis (see Appendix 7). The CI of the RE RR is completely below the responding margins of 1.29 and 1.42 and would therefore suggest that 3-monthly administration of BTAs is noninferior to the monthly administration with regards to SREs. The summary of findings is shown in Table 13.

Figure 2. Forest plot: relative risk of skeletal-related events (pooled)



Key: CI – confidence interval; RR – risk ratio.

Table 13. Summary of findings for skeletal-related events

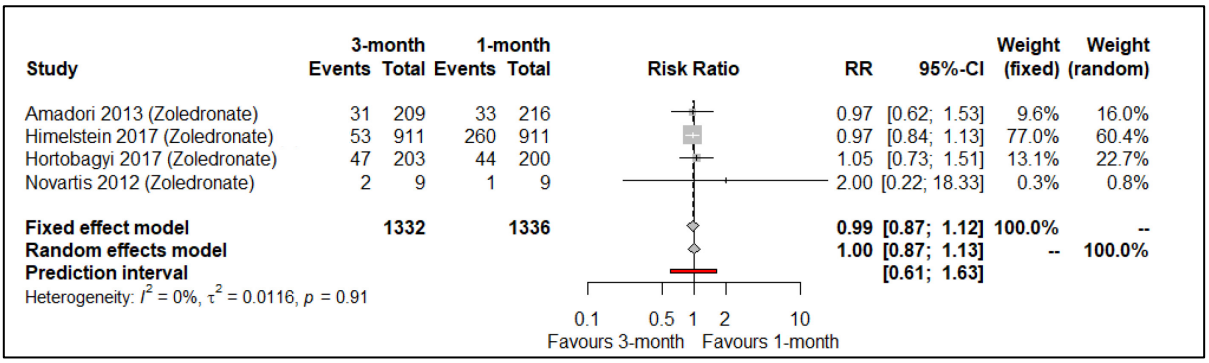
Outcome	Relative effect (95% CI)	Assumed risk 1-month[a]	Corresponding risk RE model 3-month (95% CI)[b]
SREs (pooled)	RR: 1.01 (0.82, 1.24)	24 per 100	0.25 (0.20, 0.30)

[a] Calculated as total events divided by total patients of the 1-month group.
[b] Calculated by multiplying the assumed risk with the RR and CI of the RE model.
Key: CI – confidence interval; RE – random effects; RR – risk ratio; SRE – skeletal-related event

In the sensitivity analyses, the impact of analysing data for zoledronate and denosumab separately and of including retrospective studies in the primary meta-analysis was assessed. In the latter case, 2 retrospective studies[78 82] were included (n=367). The analysis of both zoledronate and denosumab

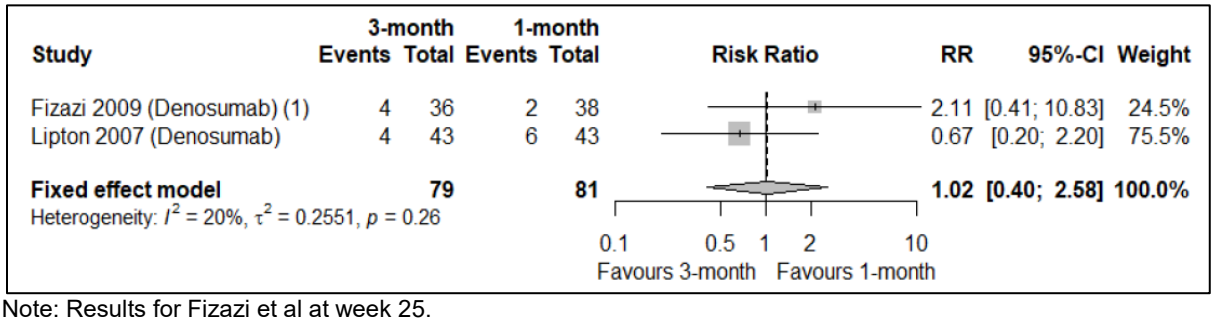
separately did not alter the results of the main analysis in terms of statistical significance (Figure 3 and Figure 4), as no significant difference is still indicated by the forest plots. The relative risk for zoledronate and denosumab using the RE model was 1.01 (95% CI: 0.82, 1.24) vs 1.00 (95% CI: 0.87, 1.13) for zoledronate alone (Figure 3) and 1.02 (95% CI: 0.40, 2.58) for denosumab alone (Figure 4). The results are driven by zoledronate, as zoledronate studies have 2,668 patients vs 160 patients for denosumab.

Figure 3. Forest plot: relative risk of skeletal-related events (zoledronate)



Key: CI – confidence interval; RR – risk ratio.

Figure 4. Forest plot: relative risk of skeletal-related events (denosumab)

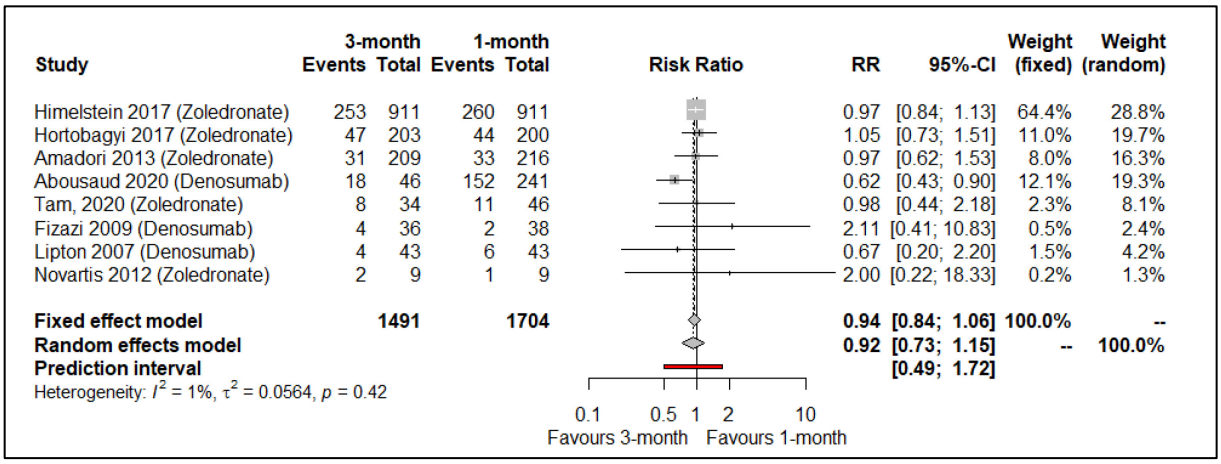


Note: Results for Fizazi et al at week 25.

Key: CI – confidence interval; RR – risk ratio.

Adding in non-RCTs results in an RR of 0.92 (95% CI: 0.73,1.15) with the RE model. Whilst still indicating no significant difference, the CIs are wider, which could again be attributed to low patient numbers.

Figure 5. Forest plot: relative risk of skeletal-related events (pooled including non-RCTs)



Key: CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio.

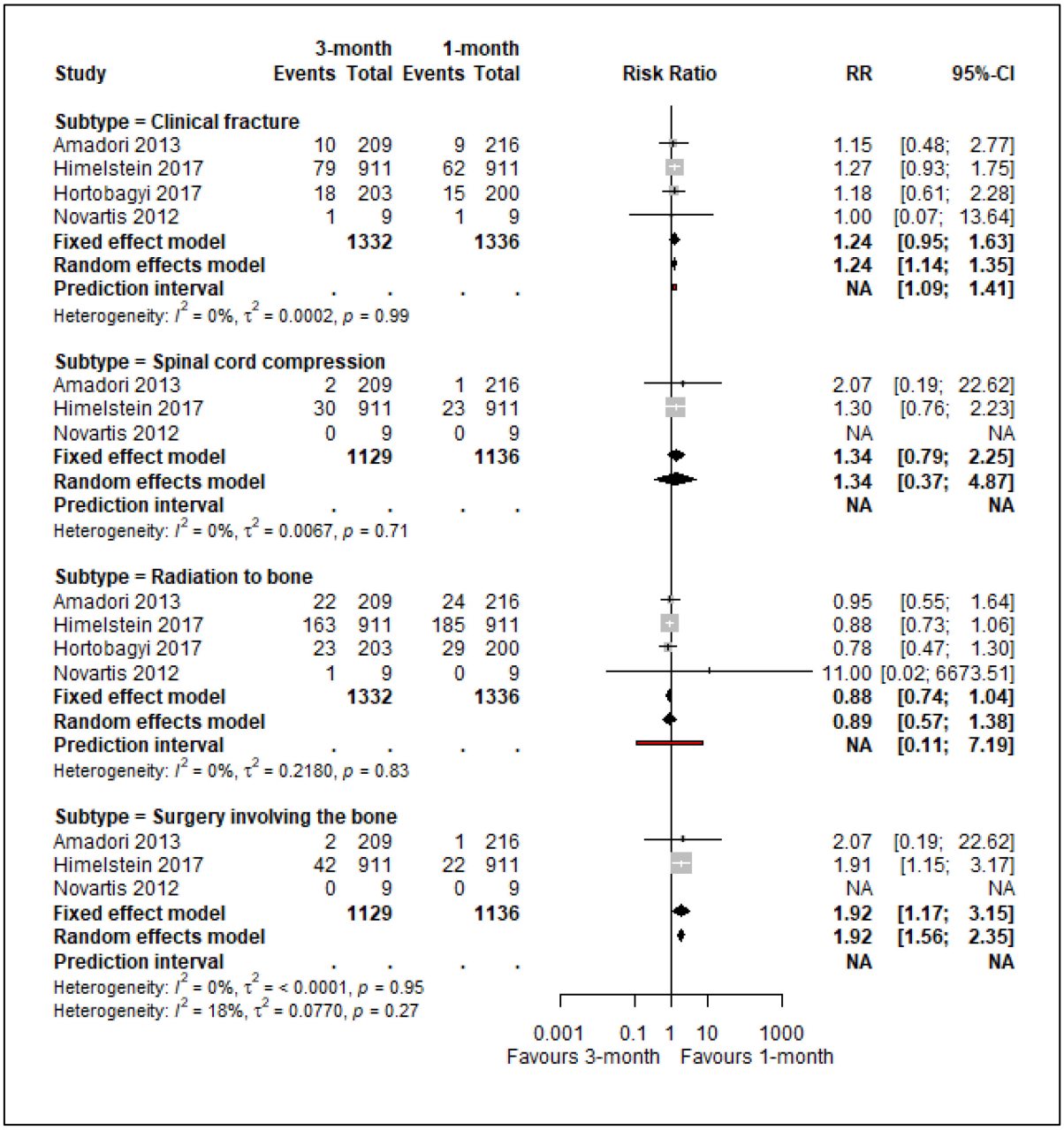
Skeletal-related events by subtype

An additional meta-analysis was conducted for each subtype of SRE to check if the overall result regarding the risk of SREs might be driven by the results of the single SRE components. Bone fractures were reported in all 4 RCTs assessing de-escalation of zoledronate (n=2,668); however, the definition of fracture slightly differed between the studies. Himelstein et al. (2017)[77] reported data on clinical fractures, but the remaining 3 studies assessed the risk of pathologic fractures. All studies reported on radiation to bone (n=2,668), while the risk of spinal cord compression and surgery involving bone was reported only by Amadori et al. (2013)[1], Himelstein et al. (2017)[77], and Novartis (2012)[76] (n=2,265).

For denosumab, Fizazi et al. (2009 and 2013)[79 80] and Lipton et al. (2007 and 2008)[2 81] reported only overall SRE risk and did not distinguish by SRE subtype. However, data on fractures, including femur fracture and pathologic fracture for the study NCT00091832 (Lipton) (n=86) and data on spinal cord compression for the study NCT00104650 (Fizazi) (n=74) were retrieved from ClinicalTrials.gov[84 85]. Due to limited data available for denosumab, the primary analysis was not conducted, but zoledronate data were meta-analysed separately (Figure 6), and a pooled analysis, including non-RCTs, was conducted (Figure 7).

Magnitude and statistical significance of the effect estimate (RR) differed between the types of SREs reported in the zoledronate studies. Clinical fracture was statistically significantly different between the treatment groups favouring monthly administration via the RE model but not statistically significant via the FE model. Surgery to bone was statistically significant via both models and favoured 1-month administration. No statistically significant difference was found for spinal cord compression and radiation to bone. Between-study heterogeneity was low in each subtype (I^2=0%). Wide CIs as a result of low event numbers make it hard to draw any definite conclusion on the effect of different dosing schedules on SRE subtypes.

Figure 6. Forest plots: relative risk of SRE subtypes (zoledronate)

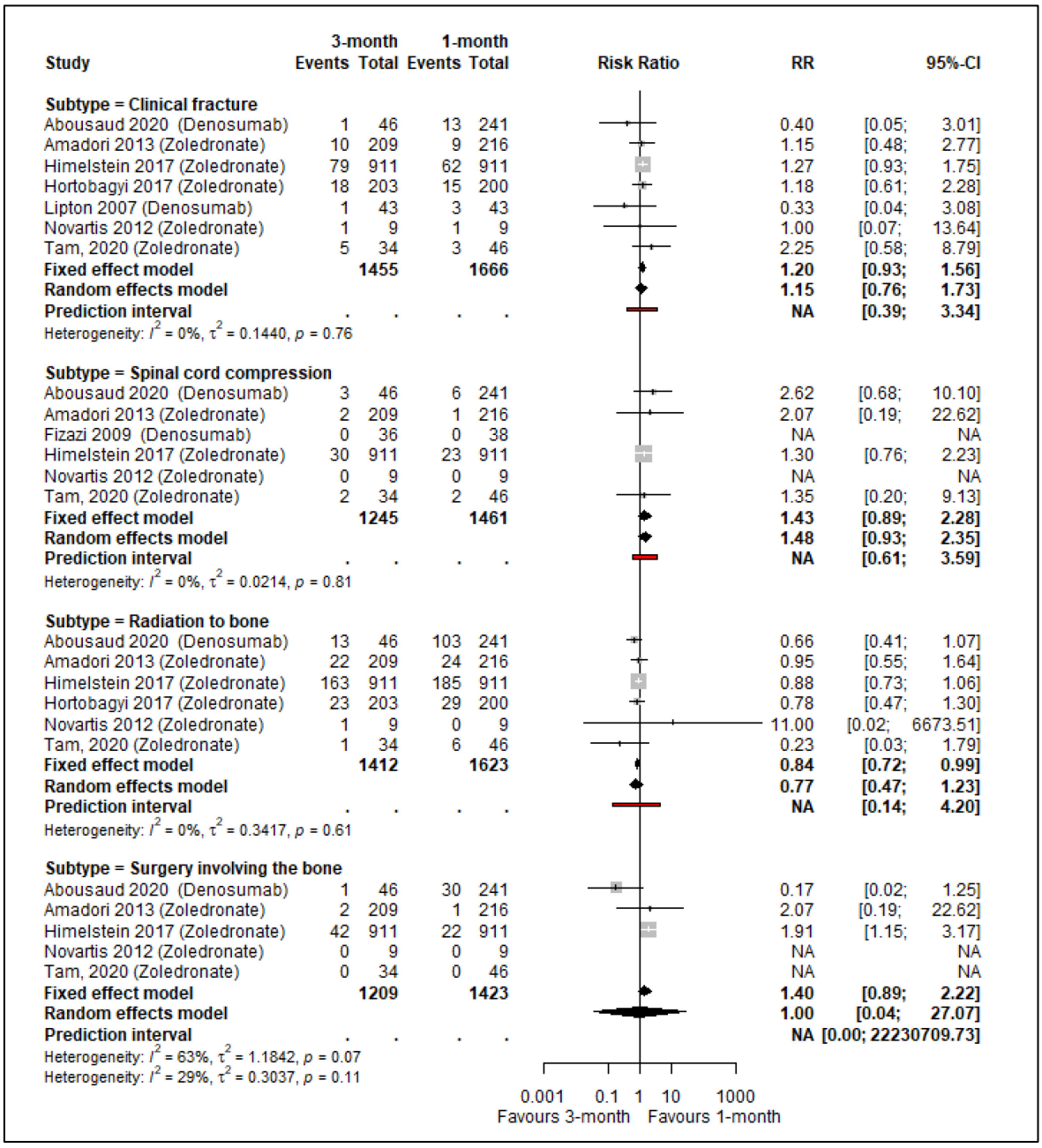


Key: CI – confidence interval; NA – not applicable; RR – risk ratio; SRE – skeletal-related event.

For denosumab, there were too few events to draw any conclusions.

When pooling zoledronate and denosumab data and including retrospective studies, differences within the subtypes were not statistically significant (Figure 7). Between-study heterogeneity within the subtypes was observed to be low (I^2=0%), except from the subtype *surgery involving bone*, which showed moderate heterogeneity (I^2=63%).

Figure 7. Forest plots: relative risk of SRE subtypes (pooled including non-RCTs)



Key: CI – confidence interval; NA – not applicable; RCT – randomized controlled trial; RR – risk ratio; SRE – skeletal-related event.

Overall, the results of the meta-analysis suggest that there are no statistically and clinically important differences in the risk of SREs between 3-monthly and monthly administration of the BTAs zoledronate and denosumab. The CI of the SRE RR ranges from 0.82 to 1.24, indicating 3-monthly dosing could range from a decrease of 18% fewer SREs to an increase of 24%. The subtype analysis showed that the overall result is not driven by single SRE types. The analysis is driven by zoledronate data of the RCTs.

Question 2: Is the 3-monthly use of BTAs safe compared to the monthly use?

Incidence of adverse events

Incidence of AEs was reported by Amadori et al. (2013)[1], Hortobagyi et al. (2017)[62], and Novartis (2012)[76] (n=843). For Himelstein et al. (2017)[77], the respective trial data were retrieved from ClinicalTrials.gov (NCT00869206)[86] (n=1,747). Data on AE incidence for denosumab were retrieved from ClinicalTrials.gov (NCT00091832[84] [Lipton] and NCT00104650[85] [Fizazi]) (n=159) since Lipton et al. (2007 and 2008) and Fizazi et al. (2009 and 2013) did not report any AEs.

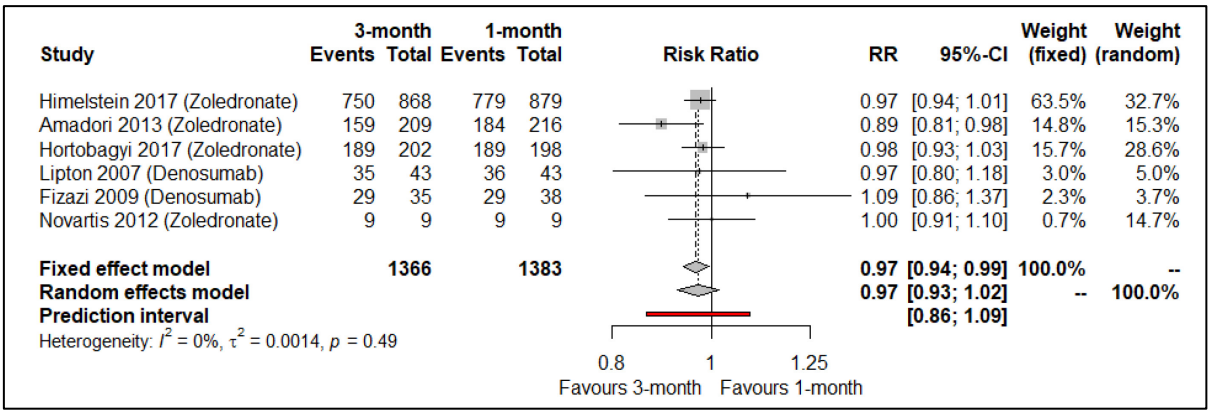
The risk of any type of AE is high; Table 14, which shows absolute risk, demonstrates a high incidence of AEs, ranging from 75% to 100% with 3-monthly dosing and from 85% to 100% with monthly BTA dosing.

Table 14. Absolute risk of AEs of the studies included in the meta-analysis

Study	Absolute risk	
	3-monthly	monthly
Himelstein et al. 2017[77]	86%	89%
Amadori et al. 2013[1]	76%	84%
Hortobagyi et al. 2017[62]	94%	95%
Lipton et al. 2007[2 81]	81%	84%
Fizazi et al. 2009[79 80]	83%	97%
Novartis 2012[76]	100%	100%

When synthesizing the data, no statistically significant difference in AE incidence was found between the 3-monthly and monthly administration of BTAs (RE: RR: 0.97; 95% CI: 0.93, 1.02) in the main analyses. However, the CI of the FE model indicates a marginally statistically significant difference favouring the 3-monthly administration (FE: RR: 0.97; 95% CI: 0.94, 0.99) (prediction interval: 0.86, 1.09) (Figure 8). The results suggest that 3-monthly use of BTAs may lead to a reduction in AEs of up to 7% or an increase of up to 2%. Heterogeneity between the studies was low (I^2=0%). The summary of findings is shown in Table 15.

Figure 8. Forest plot: relative risk of adverse events (pooled)



Key: CI – confidence interval; RR – risk ratio.

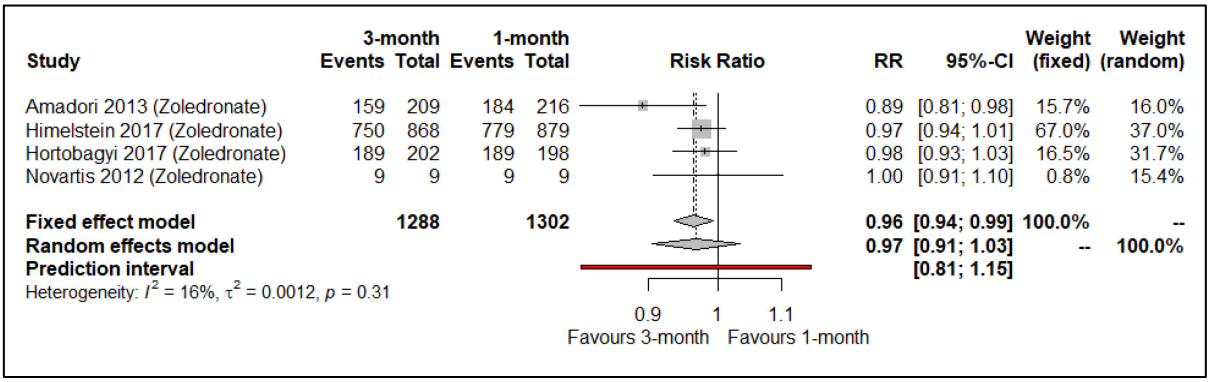
Table 15. Summary of findings for adverse events

Outcome	Relative effect (95% CI)	Assumed risk 1-month[a]	Corresponding risk RE model 3-month (95% CI)[b]
AEs (pooled)	RR: 0.97 (0.93, 1.02)	87 per 100	0.86 (0.82, 0.90)

[a] Calculated as total events divided by total patients of the 1-month group.
[b] Calculated by multiplying the assumed risk with the RR and CI of the RE model.
Key: AE – adverse event; CI – confidence interval; RE – random effects; RR – risk ratio.

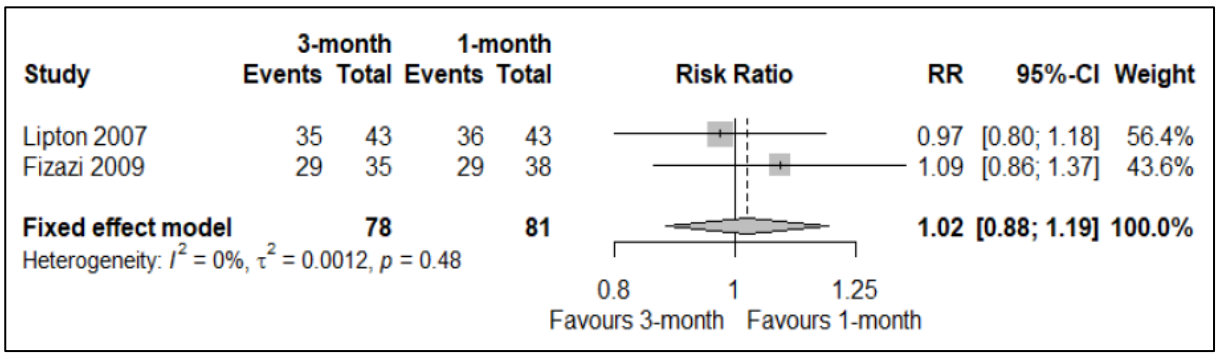
When analysing data for zoledronate and denosumab separately, no statistically significant difference was found between 3-monthly and monthly administration with the RE model (zoledronate) or the FE model (denosumab) (Figure 9 and Figure 10). When applying the FE model to the analysis including only studies assessing zoledronate, the difference between the 2 treatment groups narrowly favoured the 3-monthly administration. For the retrospective studies, no data on AEs were reported; thus, the respective sensitivity analysis was not conducted.

Figure 9. Forest plot: relative risk of adverse events (zoledronate)



Key: CI – confidence interval; RR – risk ratio.

Figure 10. Forest plot: relative risk of adverse events (denosumab)



Key: CI – confidence interval; RR – risk ratio.

Overall, no statistically significant differences in AE incidence between 3-monthly and monthly administration of BTAs were found, with the CI for AE incidence RR ranging from 0.93 to 1.02.

Incidence of serious adverse events

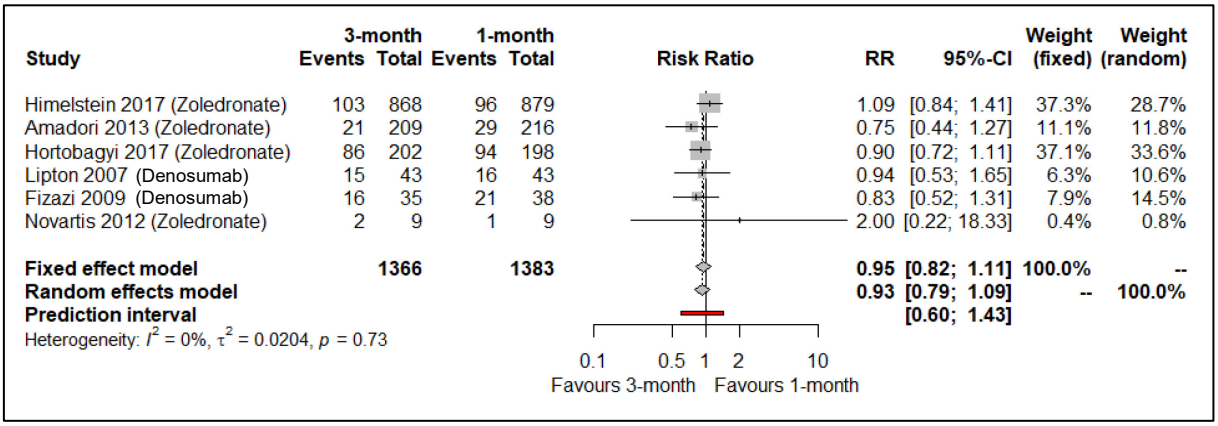
The incidence of SAEs for zoledronate was reported by Amadori et al. (2013)[1], Hortobagyi et al. (2017)[62], and Novartis (2012)[76] (n=843). For Himelstein et al. (2017)[77], the respective trial data was retrieved from ClinicalTrials.gov (NCT00869206)[86] (n=1,747). For denosumab, data on SAEs were retrieved from ClinicalTrials.gov (NCT00091832 [Lipton][84] and NCT00104650 [Fizazi][85]) (n=159).

Table 16. Absolute risk of SAEs of the studies included in the meta-analysis

Study	Absolute risk	
	3-monthly	Monthly
Himelstein et al. 2017[77]	12%	11%
Amadori et al. 2013[1]	10%	13%
Hortobagyi et al. 2017[62]	43%	47%
Lipton et al. 2007[2 81]	35%	37%
Fizazi et al. 2009[79 80]	46%	70%
Novartis 2012[76]	22%	11%

The absolute risk of an SAE ranges from 10% to 46% with 3-monthly dosing and from 11% to 70% for monthly dosing (Table 16). There were no statistically significant differences in RRs of SAEs between the 3-monthly and the monthly dosing regimens (RE: RR: 0.93; 95% CI: 0.79, 1.09; FE: RR: 0.95; 95% CI: 0.82, 1.11; prediction interval: 0.60, 1.43) (Figure 11). The CI of the point estimate suggests that a 3-monthly administration in comparison with a monthly administration may reduce the risk of SAEs by up to 21% or increase the risk of SREs by up to 9%. Between-study heterogeneity was low (I^2=0%). The summary of findings for SAEs is shown in Table 17.

Figure 11. Forest plot: relative risk of serious adverse events (pooled)



Key: CI – confidence interval; RR – risk ratio.

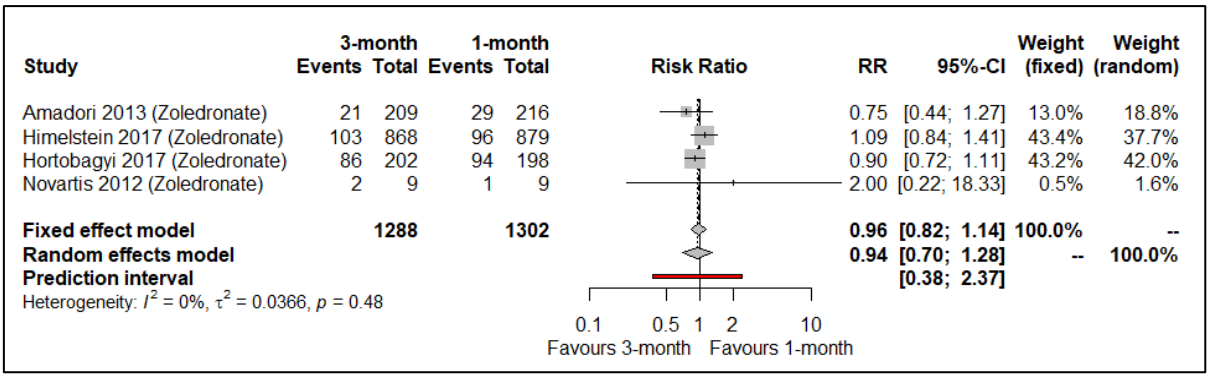
Table 17. Summary of findings for serious adverse events

Outcome	Relative effect (95% CI)	Assumed risk 1-month[a]	Corresponding risk RE model 3-month (95% CI)[b]
SAEs (pooled)	RR: 0.93 (0.79, 1.09)	19 per 100	0.17 (0.15, 0.20)

[a] Calculated as total events divided by total patients of the 1-month group.
[b] Calculated by multiplying the assumed risk with the RR and CI of the RE model.
Key: CI – confidence interval; RE – random effects; RR – risk ratio; SAE – serious adverse event

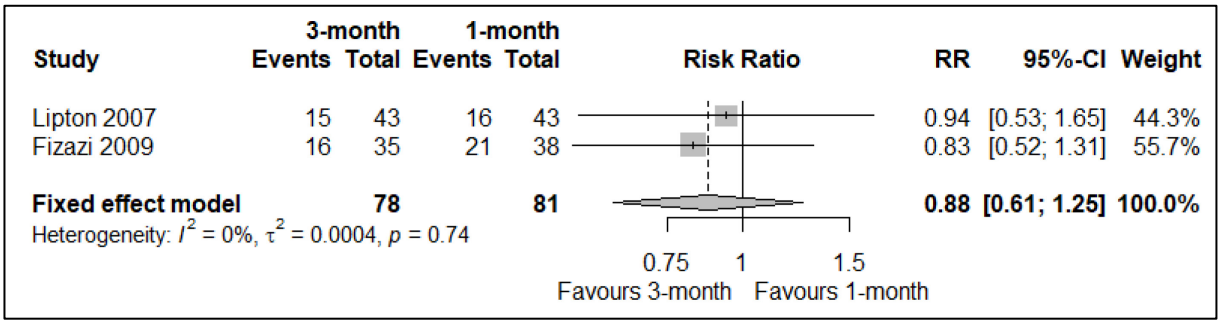
When data for zoledronate and denosumab were analysed separately, no statistically significant difference between the 3-monthly and the monthly administration was found in terms of incidence of SAEs (Figure 12 and Figure 13). Tam et al. (2020)[78] and Abousaud et al. (2020)[82] did not report incidence of SAEs; thus, a sensitivity analysis including retrospective studies was not conducted.

Figure 12. Forest plot: relative risk of serious adverse events (zoledronate)



Key: CI – confidence interval; RR – risk ratio.

Figure 13. Forest plot: relative risk of serious adverse events (denosumab)



Key: CI – confidence interval; RR – risk ratio.

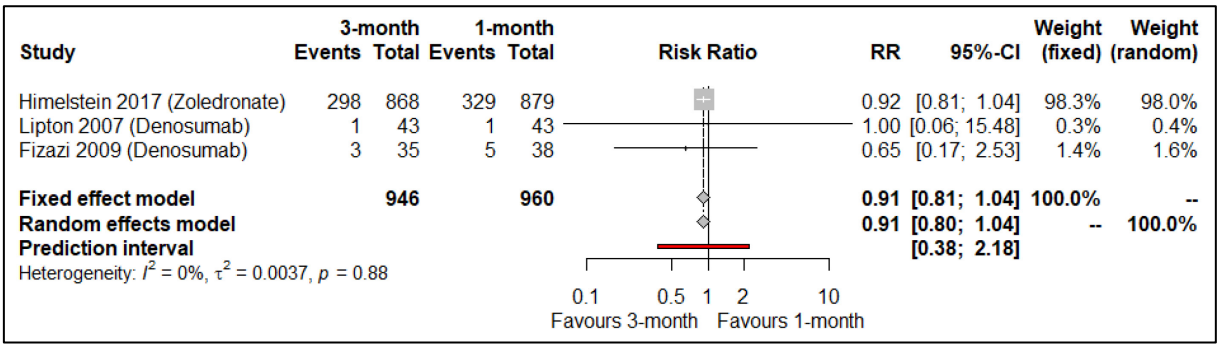
Overall, 3-monthly administration of the analysed BTAs appears to be as safe as monthly administration in terms of SAEs. The CI of SAE incidence RR ranges from 0.79 to 1.09.

Hypocalcaemia

Himelstein et al. (2017)[77] was the only study reporting data on hypocalcaemia occurring during zoledronate treatment (n=1,747). The risk of hypocalcaemia for denosumab was retrieved from

ClinicalTrials.gov for the respective studies (NCT00091832 [Lipton][84] and NCT00104650 [Fizazi][85]) (n=159). Pooling of data for zoledronate and denosumab did not result in a statistically significant difference between 3-monthly and monthly administration of BTAs (RE: RR: 0.91; 95% CI: 0.80, 1.04) (FE: RR: 0.91; 95% CI: 0.81, 1.04) (prediction interval: 0.38, 2.18) (Figure 14). The difference was not statistically significant, and between-study heterogeneity was low (I^2=0%). The results show that a 3-monthly administration of BTAs in comparison to a monthly administration may lead to a reduction in hypocalcaemia of up to 20% or to an increase of up to 4%.

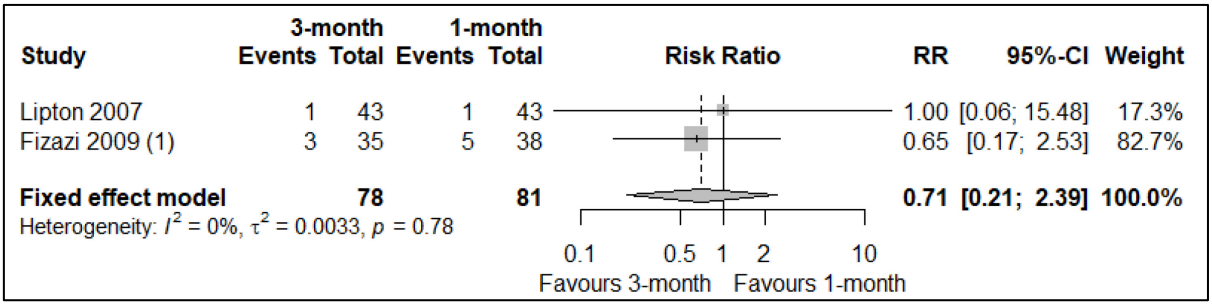
Figure 14. Forest plot: relative risk of hypocalcaemia (pooled)



Key: CI – confidence interval; RR – risk ratio.

Since there was only 1 study[77] reporting on hypocalcaemia occurrence with zoledronate treatment, a separate meta-analysis was not conducted for zoledronate. For denosumab, there was no statistically significant difference in hypocalcaemia risk between the 3-monthly and the monthly administration (Figure 15). Heterogeneity between the studies was low (I^2=0%).

Figure 15. Forest plot: relative risk of hypocalcaemia (denosumab)



Note: Fizazi et al. reported serious and non-serious results.

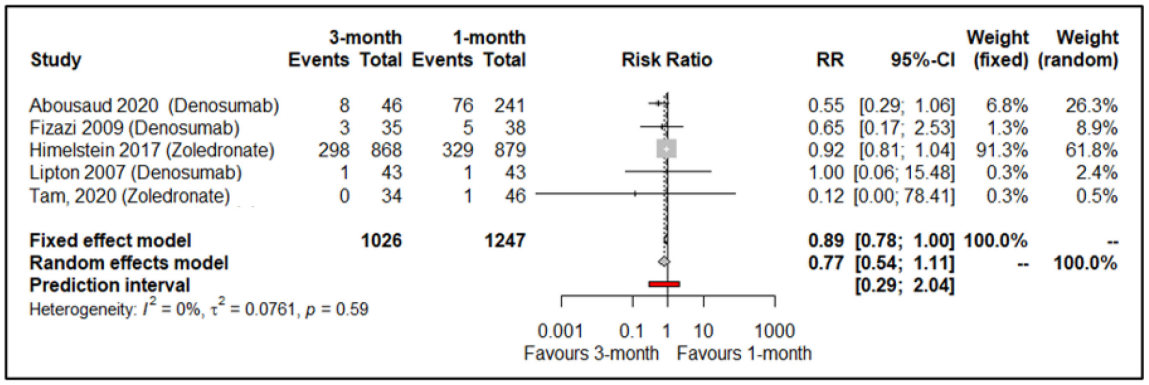
Key: CI – confidence interval; RR – risk ratio.

Both retrospective studies[78 82] reported the risk of hypocalcaemia during zoledronate and denosumab treatment, respectively (n=367). Inclusion of these data in a sensitivity analysis did not have any effect on the results of the main analysis (Figure 16).

Overall, the difference in the occurrence of hypocalcaemia in patients treated 3-monthly or monthly with BTAs is not statistically significant, although 3-monthly administration may reduce hypocalcaemia by up

to 20%. The CI of the RR in hypocalcaemia ranges from 0.8 to 1.04. However, the results need to be interpreted with caution due to the limited number of studies included. Reduced risk in patients treated with 3-monthly BTAs needs to be confirmed.

Figure 16. Forest plot: relative risk of hypocalcaemia (pooled including non-RCTs)



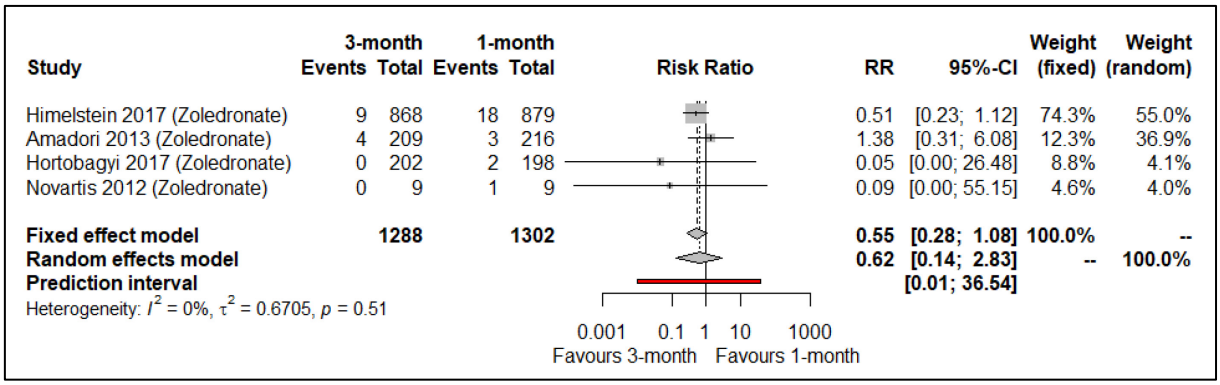
Footnotes: Tam et al. reported serious and non-serious results.

Key: CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio.

Osteonecrosis of the jaw

All 4 RCTs assessing de-escalation of zoledronate reported the risk of ONJ in patients being treated 3-monthly or monthly (n=2,590)[1 62 76 77]. However, Lipton et al. (2007 and 2008)[2 81] and Fizazi et al. (2009 and 2013)[79 80] both reported that no cases of ONJ were observed in the respective study population treated with denosumab (86 patients and 73 patients, respectively). Therefore, the main analysis was not conducted. Assessing zoledronate data separately, the RR favoured the 3-monthly administration; however, the difference was not found to be statistically significant (RE: RR: 0.62; 95% CI: 0.14, 2.83; FE: RR: 0.55; 95% CI: 0.28, 1.08; prediction interval: 0.01, 36.54) (Figure 17). Between-study heterogeneity was low (I^2=0%).

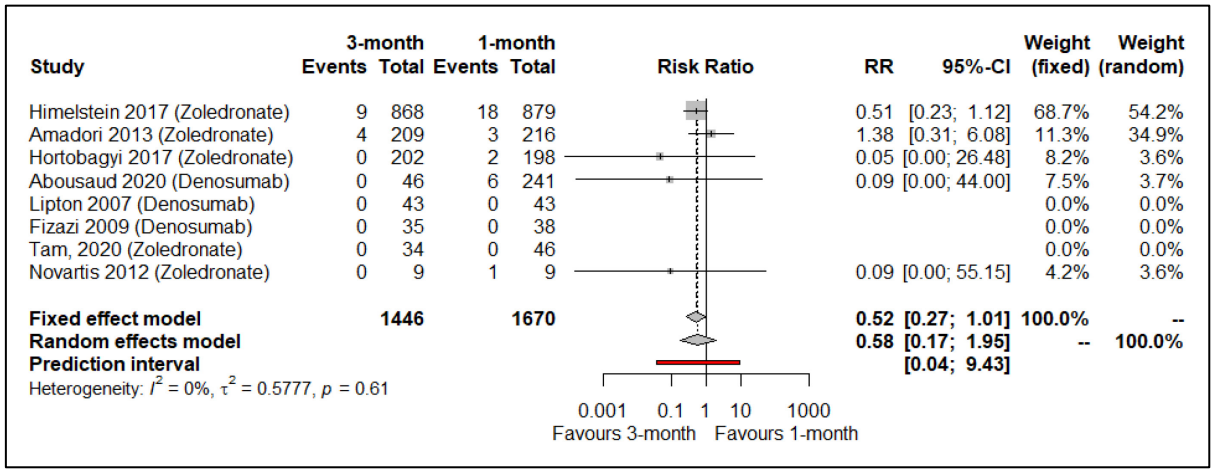
Figure 17. Forest plot: relative risk of osteonecrosis of the jaw (zoledronate)



Key: CI – confidence interval; RR – risk ratio.

The risk of ONJ was reported in both retrospective studies[78 82] (n=367) and included in the sensitivity analysis. Including data from non-RCTs did not markedly change the results from the primary analysis (RE: RR: 0.58; 95% CI: 0.17, 1.95; FE: RR: 0.52; 95% CI: 0.27, 1.01; prediction interval: 0.04, 9.43) (Figure 18). Between-study heterogeneity was low (I^2=0%).

Figure 18. Forest plot: relative risk of osteonecrosis of the jaw (pooled and non-RCTs)



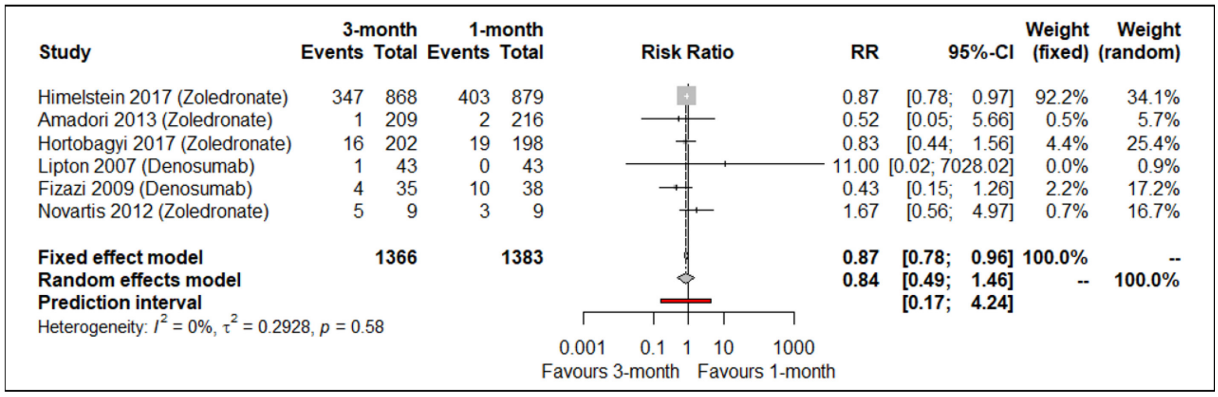
Key: CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio.

Although differences in the risk of ONJ are not statistically significantly different between the 3-monthly and monthly administration of zoledronate and denosumab, the CIs are wide and the RR favours 3-monthly administration The clinical importance of these findings needs to be examined further.

Renal adverse events

Amadori et al. (2013)[1], Hortobagyi et al. (2017)[62], and Novartis (2012)[76] reported RAEs for zoledronate, and data for the study by Himelstein et al. (2017) were retrieved from ClinicalTrials.gov (NCT00869206)[86] (n=2,590). For denosumab, data on RAEs were retrieved from ClinicalTrials.gov (NCT00091832 [Lipton][84] and NCT00104650 [Fizazi][85]) (n=159). However, definitions of RAEs differed between the studies as described in Table 9 and Table 11. Using the RE model, there was no significant difference between 3-monthly and monthly administration of BTAs (RE: RR: 0.84; 95% CI: 0.49, 1.46), but the FE model favoured 3-monthly administration (FE: RR: 0.87; 95% CI: 0.78, 0.96) (prediction interval: 0.17, 4.24) (Figure 19). Between-study heterogeneity was low (I^2=0%). The CI of the point estimate indicates that 3-monthly administration of BTAs may reduce RAEs by up to 51% or increase RAEs by up to 46%.

Figure 19. Forest plot: relative risk of renal adverse events (pooled)

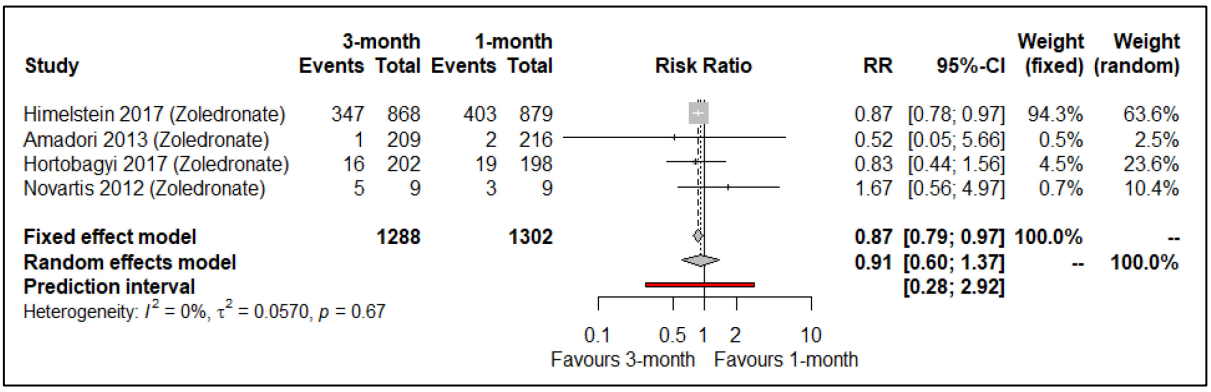


Note: Continuity correction of 0.1 was applied for studies with zero cell frequencies.

Key: CI – confidence interval; RR – risk ratio.

Separate meta-analyses of zoledronate and denosumab data did not have any impact on the results from the main analysis (Figure 20 and Figure 21). However, the FE model favoured 3-monthly administration for zoledronate.

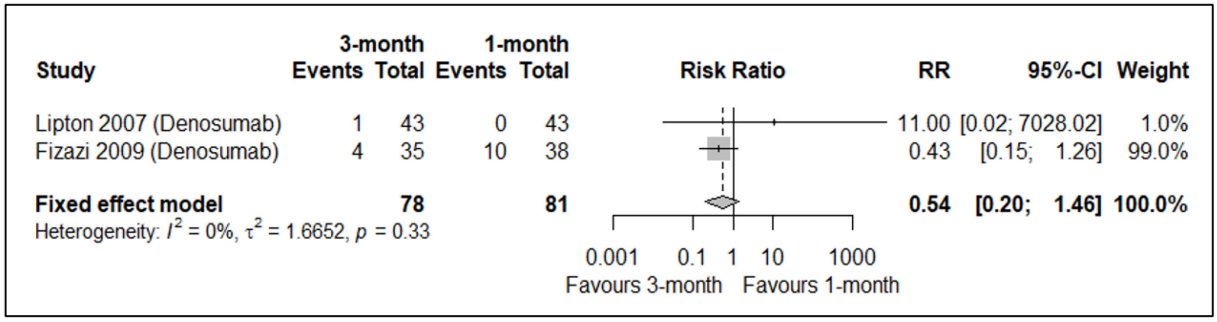
Figure 20. Forest plot: relative risk of renal adverse events (zoledronate)



Note: Continuity correction of 0.1 was applied for studies with zero cell frequencies.

Key: CI – confidence interval; RR – risk ratio.

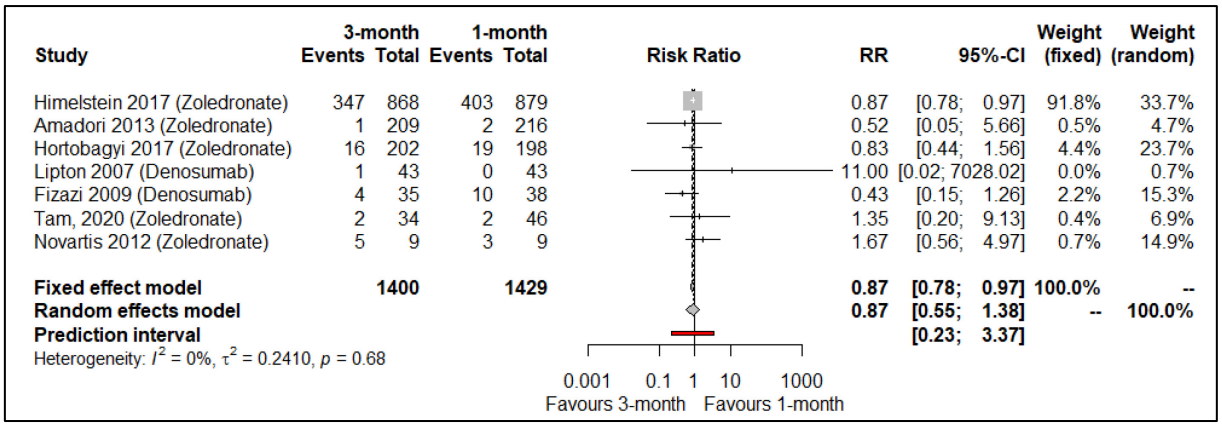
Figure 21. Forest plot: relative risk of renal adverse events (denosumab)



Key: CI – confidence interval; RR – risk ratio.

Tam et al. (2020)[78] reported the incidence of RAEs, which were defined as Common Terminology Criteria for Adverse Events (CTCAE) grade 2 kidney dysfunctions (Table 9) (n=80). Data were included in the sensitivity analysis, which was found to have no marked effect on the previous results (RE: RR: 0.87; 95% CI: 0.55, 1.38; prediction interval: 0.23, 3.37) (Figure 22). However, when applying the FE model, results favoured 3-monthly dosing. Between-study heterogeneity was low (I^2=0%).

Figure 22. Forest plot: relative risk of renal adverse events (pooled including non-RCT)



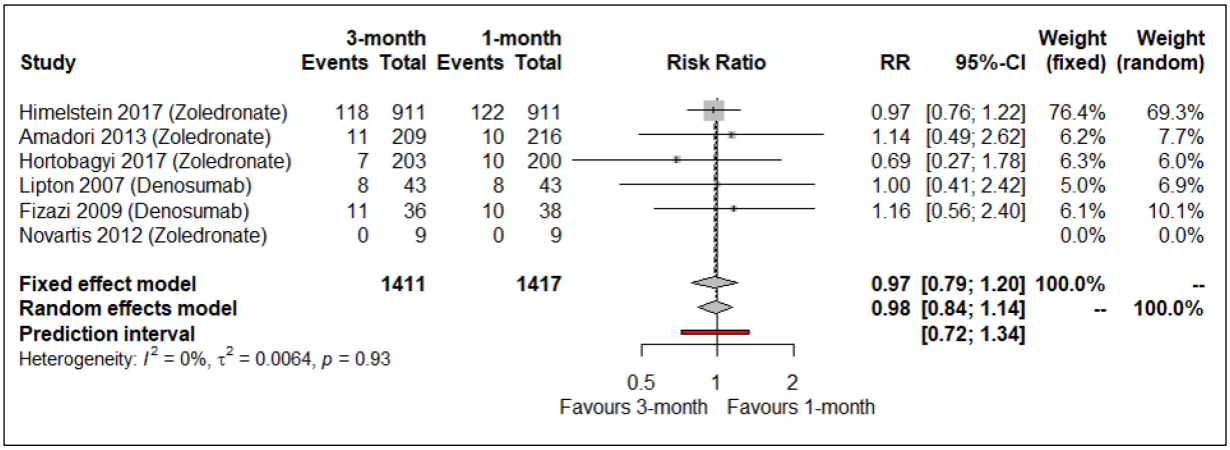
Key: CI – confidence interval; RCT – randomized controlled trial; RR – risk ratio.

Overall, there is no statistically significant difference between 3-monthly and monthly administration of BTAs in terms of incidence of RAEs. However, the CI of the RAE RR ranged from 0.49 to 1.46, so it remains unclear if 3-monthly administration is favoured from a clinical perspective.

Mortality

Overall mortality was reported for 3 RCTs and on-treatment deaths for 1 RCT assessing de-escalation of zoledronate[1 62 76 77] (n=2,668). For denosumab, overall mortality was reported on ClinicalTrials.gov (NCT00091832 [Lipton][84] and NCT00104650 [Fizazi][85]) (n=159). When synthesizing the data, no statistically significant difference was found between the 3-monthly and the monthly administration (RE: RR: 0.98; 95% CI: 0.84, 1.14) (FE: RR: 0.97; 95% CI: 0.79, 1.20) (prediction interval: 0.72, 1.34) (Figure 23). The CI of the point estimates indicates that 3-monthly administration of BTAs may lead to a reduction in overall mortality by up to 16% or an increase by up to 14%. Heterogeneity between the studies was low (I^2=0%).

Figure 23. Forest plot: relative risk of overall mortality (pooled)

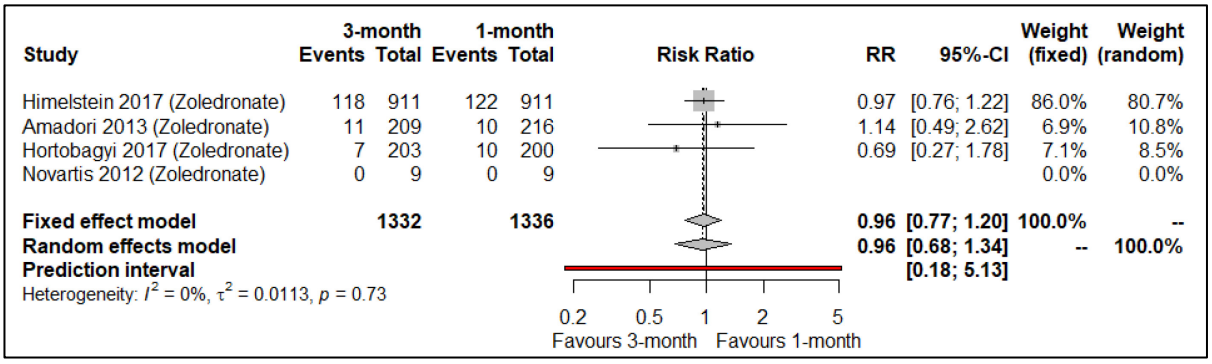


Note: Hortobagyi 2017 reported on-treatment deaths.

Key: CI – confidence interval; RR – risk ratio.

Separate analyses of zoledronate and denosumab data on mortality did not have an impact on the results from the main analysis (Figure 24 and Figure 25).

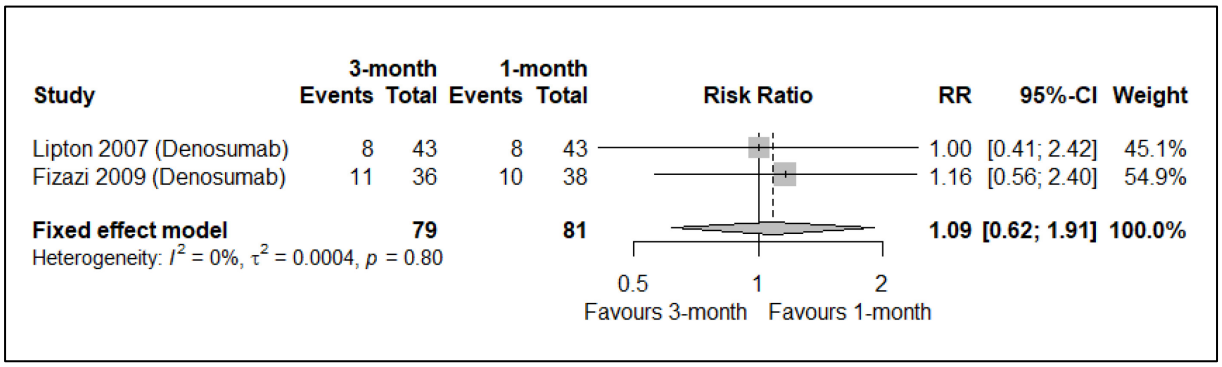
Figure 24. Forest plot: relative risk of overall mortality (zoledronate)



Note: Hortobagyi 2017 reported on-treatment deaths.

Key: CI – confidence interval; RR – risk ratio.

Figure 25. Forest plot: relative risk of overall mortality (denosumab)



Key: CI – confidence interval; RR – risk ratio.

Tam et al. (2020)[78] and Abousaud et al. (2020)[82] did not provide any information on on-treatment deaths. Thus, a sensitivity analysis including retrospective studies could not be conducted.

Overall, there is no evidence that increasing the time between zoledronate and denosumab administrations would have a significant impact on mortality. The CI of overall mortality RR ranges from 0.84 to 1.14.

Summary statement of efficacy, effectiveness, and safety

Nine studies formed the evidence base for the evaluation by meta-analysis of the efficacy, effectiveness, and safety of 3-monthly dosing with BTAs compared to monthly dosing (RCT=7; non-RCT=2). Available data were restricted to zoledronate and denosumab, as no data were retrieved for ibandronate. Independently of the method applied for the meta-analysis, the results indicated no statistically significant difference between dosing regimens on the risk of SREs, which was confirmed by different sensitivity analyses. The results suggest that an introduction of a 3-monthly administration of BTAs may lead to a reduction in SREs of up to 18% or an increase in SREs of up to 24%. When analysing subtypes of SREs separately, the RE model analysis found statistically significant differences in the risk of clinical fractures and surgery to bone favouring the monthly administration. However, application of the FE model had an impact on the width of the CIs and, ultimately, led to insignificant results in the case of clinical fractures. Analysis of AEs did not result in a statistically significant difference between both dosing regimens when looking at the results of the RE model. The results from the RE model indicate a reduction in AEs by 7% or an increase by 2% with a 3-monthly administration of AEs. There was no significant difference in the risk of SAEs either with the RE model CIs showing a potential decreased risk of 21% versus a potential increased risk of 9%. Thus, a 3-monthly administration may lead to a benefit in reducing SAEs by up to 21% while increasing SREs by up to 24%. The summary of findings for the primary outcomes is shown in Table 18.

Table 18. Summary of findings for the primary outcomes

Outcome	Relative effect (95% CI)	Assumed risk 1-month[a]	Corresponding risk RE model 3-month (95% CI)[b]
SREs (pooled)	RR: 1.01 (0.82, 1.24)	24 per 100	0.25 (0.20, 0.30)
AEs (pooled)	RR: 0.97 (0.93, 1.02)	87 per 100	0.86 (0.82, 0.90)
SAEs (pooled)	RR: 0.93 (0.79, 1.09)	19 per 100	0.17 (0.15, 0.20)

[a] Calculated as total events divided by total patients of the 1-month group.

[b] Calculated by multiplying the assumed risk with the RR and CI of the RE model.

Key: AE – adverse event; CI – confidence interval; RE – random effects; RR – risk ratio; SAE – serious adverse event; SRE – skeletal-related event.

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8 Costs, cost-effectiveness, and budget impact

8.1 Methodology for costs, cost-effectiveness, and budget impact

8.1.1 Databases and search strategy

The database search for evidence on costs, cost-effectiveness, and budget impact was conducted together with the search for clinical evidence as described in Section 7.1.1. Results of the health economic literature search were extracted based on key health economic study characteristics (Section 8.2.2), evaluated by the Consensus Health Economics Checklist (CHEC) (Section 8.1.3), and summarized (Section 8.2.3).

8.1.2 Other sources

In addition to the databases search via OVID, a hand search for literature on costs, cost-effectiveness, and budget impact was performed as described in Section 7.1.2.

To search for previous assessments of the present research question, websites of the following national HTA agencies were consulted:

- Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), Germany
- Canadian Agency for Drugs and Technologies in Health (CADTH), Canada
- Haute Autorité de Santé (HAS), France
- National Institute for Health and Care Excellence (NICE), United Kingdom
- Institute of Technology Assessment / HTA Unit, Austria
- Health Council of the Netherlands (Gezondheidsraad), the Netherlands
- Centre for Medical Health Technology Assessment, Sweden
- Institute for Clinical and Economic Review, United States
- Health Technology Assessment Agency / Institute for Health “Carlos III”, Spain

8.1.3 Assessment of quality of evidence

The quality analysis of the cost-effectiveness study was conducted using the CHEC. The CHEC is a 19-item checklist with questions regarding the economic evaluation that can be answered with “yes” and “no.” In the case of insufficient available data, the answer “no” was chosen (see Appendix 8).[87]

8.1.4 Methodology for health economic analyses

Modelling approach

Based on the results from the meta-analysis, a de novo budget impact model and a cost-comparison model were developed using Excel to estimate the budget impact and direct cost per patient of 3-monthly BTA administration compared with monthly administration in patients with BM from the perspective of a Swiss payer. The rationale for conducting a budget impact and cost-comparison analysis and not a cost-effectiveness study was because no compelling data were found for differences in efficacy.

1. The results from the main meta-analysis using an RE model suggested that there was no statistically significant difference in efficacy or AEs for the 2 dosing schedules.
2. Only 1 cost-effectiveness study (Shapiro 2017)[88] was identified from searching the databases. This compared monthly zoledronate and denosumab with 3-monthly zoledronate treatment; effectiveness data for 3-monthly denosumab treatment is not available.
3. Results of this study showed that monthly zoledronate vs 3-monthly zoledronate treatment resulted in 0.90 and 0.91 QALYs in year 1 and 0.91 and 0.91 QALYs in year 2, respectively. Therefore, the effectiveness comparing 3-monthly vs monthly treatment could be considered equivalent.

The models were conducted to provide a valid computing framework that allows users to understand the relation between monthly BTA treatment and the possible budget consequences of a 3-monthly BTA treatment scenario.

The incremental costs were calculated as the difference between 3-monthly BTA treatment compared to monthly BTA treatment. Component costs included treatment, drug, and administration costs. The cost comparison model is at the single patient level, whereas the budget impact model is at the national level, considering the size of the population eligible for treatment. For example, the budget impact model used the following calculations to estimate the budget impact for year 1:

- Treatment costs (per treated patient) – monthly treatment
  Zoledronate = monthly zoledronate drug costs + monthly zoledronate administration costs = a
  Denosumab = monthly denosumab drug costs + monthly denosumab administration costs = b
- Treatment costs (per treated patient) – 3-monthly treatment
  Zoledronate = 3-monthly zoledronate drug costs + 3-monthly zoledronate administration costs = c
  Denosumab = 3-monthly denosumab drug costs + 3-monthly denosumab administration costs = d
- Total costs year 1 – monthly treatment
  (Incident patients year 1 * market share zoledronate * a) + (incident patients year 1 * market share denosumab * b) = e
- Total costs year 1 – 3-monthly treatment
  (Incident patients year 1 * market share zoledronate * c) + (incident patients year 1 * market share denosumab * d) = f

- Budget impact = f – e

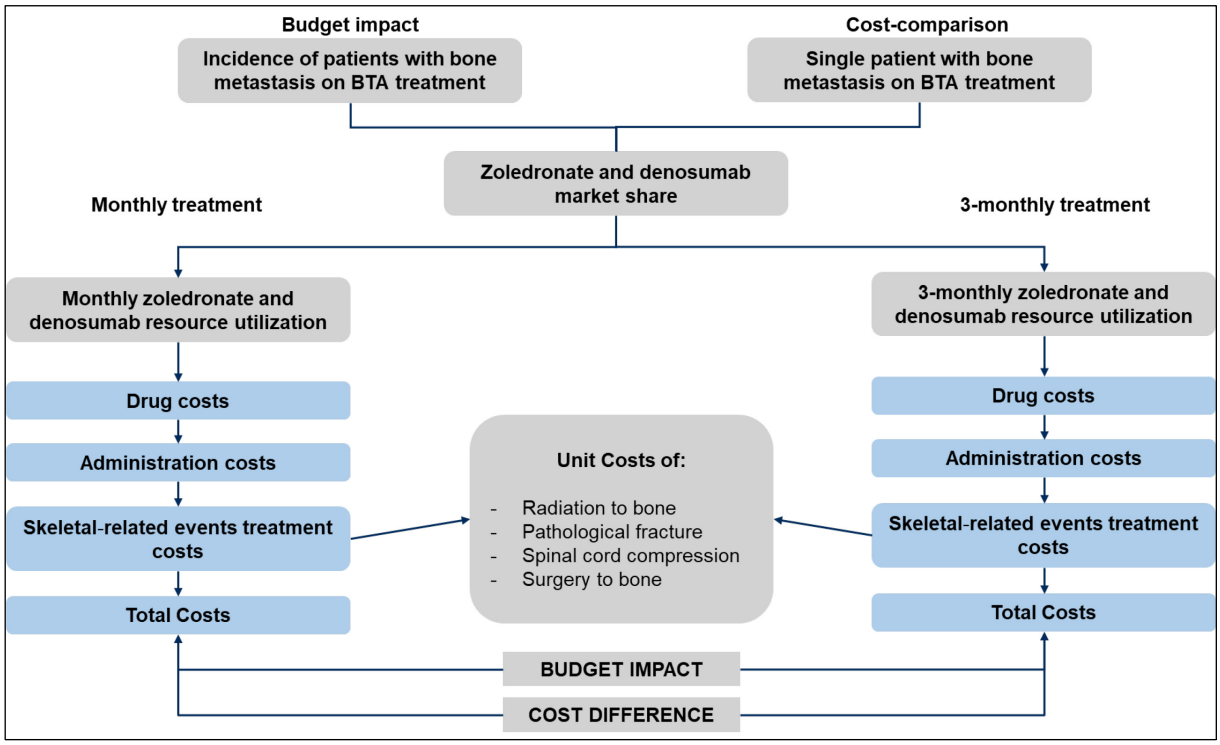
Note: At each cycle of the model, treatment costs are multiplied by the percentage of patients who remain on treatment.

For the scenario analysis, SRE costs were included. The incidence of SAEs was not part of the model due to the rarity of such events and because there is no evidence of a difference between the 3-monthly and monthly dosing intervals. Ibandronate was not included in the model, as the literature review found no clinical trials comparing 3-monthly vs monthly treatment. The schematic presentation of the budget impact and cost-comparison structure is shown in Figure 26.

Patient Population

The target patient population for the model included patients with cancer-related BM from solid tumours and patients with MM with bone involvement. The BTAs zoledronate and denosumab are used in combination with antineoplastic therapy to reduce risk of fracture and bone pain, hypercalcaemia, and tumour growth. The model compared patients with bone metastases on BTA treatment who are treated with 3-monthly zoledronate or denosumab to those patients treated monthly (i.e., 3- to 4-weekly treatment per the SmPC).[23 24 28]

Figure 26. Structure of the budget impact and cost-comparison model



Note: Market shares are based on packages sold.

Model perspective

The model was developed from a Swiss payer perspective and covered only direct treatment costs (i.e., drug and administration costs and SRE costs for the scenario analysis). Potential copayments (out of pocket) by patients were not considered. SAE and AE costs were not included in the base case analysis, as no significant difference in incidence of AEs between the 3-monthly and monthly dosing interval was identified from the main analysis. Indirect costs (lost productivity, caregiver costs, etc.) were not included in the model since the scope of the analysis was to assess the budget impact and costs per patient solely from the payer perspective.

Time horizon

For the budget impact analysis, a 5-year time horizon was used to estimate the total cost of monthly and 3-monthly BTA treatment and budget impact, consistent with recommendations from the Academy of Managed Care Pharmacy.[89] For the cost-comparison model, a 5-year time horizon was used due to the severity of the disease and estimated life expectancy. Stopeck et al. stated, “overall mean survival was 2.5 years (2.2, 3.7, and 1.7 years for prostate cancer, breast cancer, and other solid tumours, respectively) and median survival was 1.6 years (1.6, 2.8, and 0.9 years, respectively)”.[90]

Model inputs

The budget impact and cost-comparison analyses used the estimated costs over the modelled time horizon to calculate the difference in costs between the 3-monthly and the monthly BTA treatment for patients with BM. Model input descriptions follow.

Target population

The budget impact analysis was based on incidence of patients with BM from advanced cancers on BTA treatment (zoledronate and denosumab). It is assumed patients already on treatment will not change their regimen and as a result, the 3-monthly treatment interval is only relevant for new patients.

Sales data (median of 3,605 patients in year 2015) could not be used to calculate patient numbers because (1) packages sold would count for new and prevalent patients, (2) packages sold divided by the amount of injections/infusions as per SmPC do not count for the fact that some patients will have a reduced dosing frequency over time and, (3) zoledronate is used in other indications (e.g., zoledronate could be used to treat patients with hypercalcaemia).

The incidence could not be obtained from the literature, as the patient population authorised for treatment varies by country. Therefore, yearly mortality incidence was used as a proxy for metastatic disease to calculate patient numbers. Thus, incident patients were calculated as:

- Cancer mortality in Switzerland[7] multiplied by
- Incidence of bone metastases[91] multiplied by
- Percentage on BTA treatment[18] multiplied by
- Percentage on zoledronate and denosumab treatment[18]

For example, the incidence of BC patients in Switzerland with BM from metastatic disease on BTA treatment, excluding ibandronate, would be calculated as 1,506 * 73% * 80% * 94.39% = 830 patients. Yearly mortality incidence was used as a proxy for metastatic disease to calculate patient numbers.

In order to count for population growth, an annual growth rate of 1.01% was used based on the average Swiss population growth from 2015 to 2019.[92] The inputs utilized in estimating the size of the patient population and determining treatment costs are shown in Table 19 and Table 20.

Table 19. Estimated size of the eligible (incident) patient population

Primary tumour	Cancer mortality in Switzerland[a] (a)[7]	Incidence of bone metastases (b)[91]	Mortality x percentage (a*b)=c	Percentage on BTA treatment (d)[18]	Incidence x percentage (c*d)=e	Percentage on zoledronate and denosumab treatment (f)[18]	Incidence x percentage (e*f)
Breast	1,506	73%	1,099	80%	880	94.39%	830
Prostate	1,299	68%	833	73%	645	94.39%	609
Thyroid	107	42%	45	69%	31	94.39%	29
Bronchus	3,582	36%	1,290	65%	838	94.39%	791
Rectum	547	11%	60	69%	42	94.39%	39
Kidney	438	35%	153	69%	106	94.39%	100
Oesophagus	529	6%	32	69%	22	94.39%	21
Gastrointestinal tract	2,399[b]	5%	120	69%	83	94.39%	78
Sum	10,404		3,682		2,645		**2,497**

[a] Mortality was used as a proxy for metastatic disease.

[b] Lip, oral cavity, nasopharynx, oropharynx, hypopharynx, stomach, colon, anus (rectum and oesophagus already counted).

Key: BTA – bone-targeting agent.

Table 20. Estimated annual growth of the incident model population

	Current	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
Eligible incident patients	2,497	2,522	2,548	2,573	2,599	2,626	15,365

Market shares

The market share estimates represent the percentage of treated patients receiving each treatment in the monthly and 3-monthly BTA treatment arms. Current market shares are based on weighted averages based on packages sold from the Sasis COGE data pool.[93] Future market shares are assumed to stay the same over time as zoledronate is not expected to draw market share from denosumab or denosumab to draw market share from zoledronate. The market shares are shown in Table 21.

Table 21. Assumed market shares according to the Sasis COGE data pool

	Current	Year 1	Year 2	Year 3	Year 4	Year 5
Zoledronate	31%	31%	31%	31%	31%	31%
Denosumab	69%	69%	69%	69%	69%	69%
Total	100%	100%	100%	100%	100%	100%
Source: Sasis COGE data pool[93]						

Treatment discontinuation

Stopeck et al. estimated the mean BTA treatment duration.[90] Mean duration on treatment was 1.3 years (average of 1.2 years for PC, 1.9 years for BC, and 0.8 years for other solid tumours). Overall mean and median survival were 2.5 and 1.6 years, respectively. The monthly rate (hazard) to discontinue = 1/average duration of treatment (15.6 months). The exponential function was used to convert the rate to a monthly probability.

For example, the percentage of patients on-treatment in month 1 is calculated as exp(-(1/15.6)*1) = 93.79%. The first 4 months of treatment discontinuation are shown in Table 22.

Table 22. Treatment discontinuation

Month	On-treatment	Off-treatment
0	100%	0%
1	93.79%	6.21%
2	87.97%	12.03%
3	82.51%	17.49%
4	77.38%	22.62%

Treatment costs

In the budget impact analysis and the cost-comparison analysis, the annual treatment costs for the whole patient population and the average annual treatment costs per patient, respectively, were calculated for each drug regimen. Public drug prices were sourced from the “Spezialitätenliste”[46]. For denosumab, the price for the brand Xgeva was used, and zoledronate price was based on a weighted average of sales data in 2019. For zoledronate, the median dosage was used (i.e., every 3.5 weeks)

and for denosumab, dosing was every 4 weeks[23 28]. Table 24 shows the inputs used to calculate the drug costs.

Administration costs were based on general practitioner (GP) and nurse time from TARMED Catalogue[94] codes 0.0010 (first 5 minutes of consultation), 0.0020 (each addition 5 minutes of consultation for people 6–70 years of age), 0.137 (monitoring for people 6–75 years of age for each 15 minutes), and 0.0855 (vascular access, peripheral venous, any access, by non-medical personnel).

Zoledronate infusion should be administered over at least 15 minutes per the SmPC.[23] A total of 10 minutes of consultation and 30 minutes of monitoring was assumed for the administration of a zoledronate infusion. For the denosumab SC injection, a 15-minute GP visit was assumed.[95] Administration costs were sourced from a recent HTA report[95]. In order to determine whether the administration costs were still consistent, the latest TARMED[94] and "taxpunktwert"[96] were consulted. The inputs utilized in estimating the administration costs are shown in Table 25.

Annual drug costs were calculated based on cost per unit, doses per year, and cost of administration per dose. The annual drug costs were calculated as:

- The cost per unit multiplied by
- The doses per year multiplied by
- The annual percentage of patients on treatment, described in the treatment discontinuation paragraph

Skeletal-related events costs

The probability (i.e., risk) of first and subsequent SREs was based on data reported in the prescribing information and pivotal trials (Xgeva prescribing information 2020[28], studies 20050136, 20050244, 20050103). The probability of an SRE was assumed to stay the same over time (i.e., constant hazard model) because detailed data of event occurrences were not available among those who survive. Furthermore, median time to SRE in the 3 studies (20050136, 20050244, 20050103) ranged between 16.3 to 26.4 months, and the median time to SRE was not reached in the denosumab arm in one of the studies (20050136).

Subsequent SREs were assumed to have the same distribution as first SRE. The following formulas were used to estimate the annual SRE probabilities:

- Number of SREs, including subsequent SRE = total number of patients * first and subsequent SRE (mean) * distribution of first SRE
- Monthly rate of an SRE for each arm = -(LN(1-(number of first and subsequent SREs / total number of patients))) / study duration

- Based on the monthly rate for each arm, an average rate of the 3 trials of an SRE for zoledronate and denosumab was calculated
- Annual probability zoledronate or denosumab SRE = 1-EXP(-average rate of an SRE of zoledronate or denosumab*1)

Pivotal trial information that was used to calculate annual SRE probabilities is shown in Appendix 9.

Cost per AE was based on unit costs from a Swiss perspective of a health economic study.[97] In order to convert SRE costs to 2020 CHF, exchange rates[97] and the healthcare component of inflation rates were used.[98] The exchange rate to convert Euro to CHF was 1.20 in 2012. Inflation rates of the healthcare component in 2012 and 2020 were 102.4 and 97.32, respectively, resulting in an inflation rate of 0.950 (97.32/102.4). At the time of the analyses (March 2021), the most recent exchange rate was for 2020.

SRE costs were included in the scenario sensitivity analysis only, as the meta-analysis did not show a significant difference between the 3-monthly and monthly dosing interval.

Sensitivity analysis

Univariate sensitivity analyses were conducted to test the sensitivity of the model variations in the model parameters by varying individual parameters over a range between ±10%. This procedure allows determination of the parameters with the greatest impact on the budget impact and cost comparison.

8.2 Results for costs, cost-effectiveness, and budget impact

Search and selection regarding costs, budget impact, and cost-effectiveness were conducted in Medline, Embase, and EBMR, which includes the databases CDSR, DARE, HTA, and NHSEED.

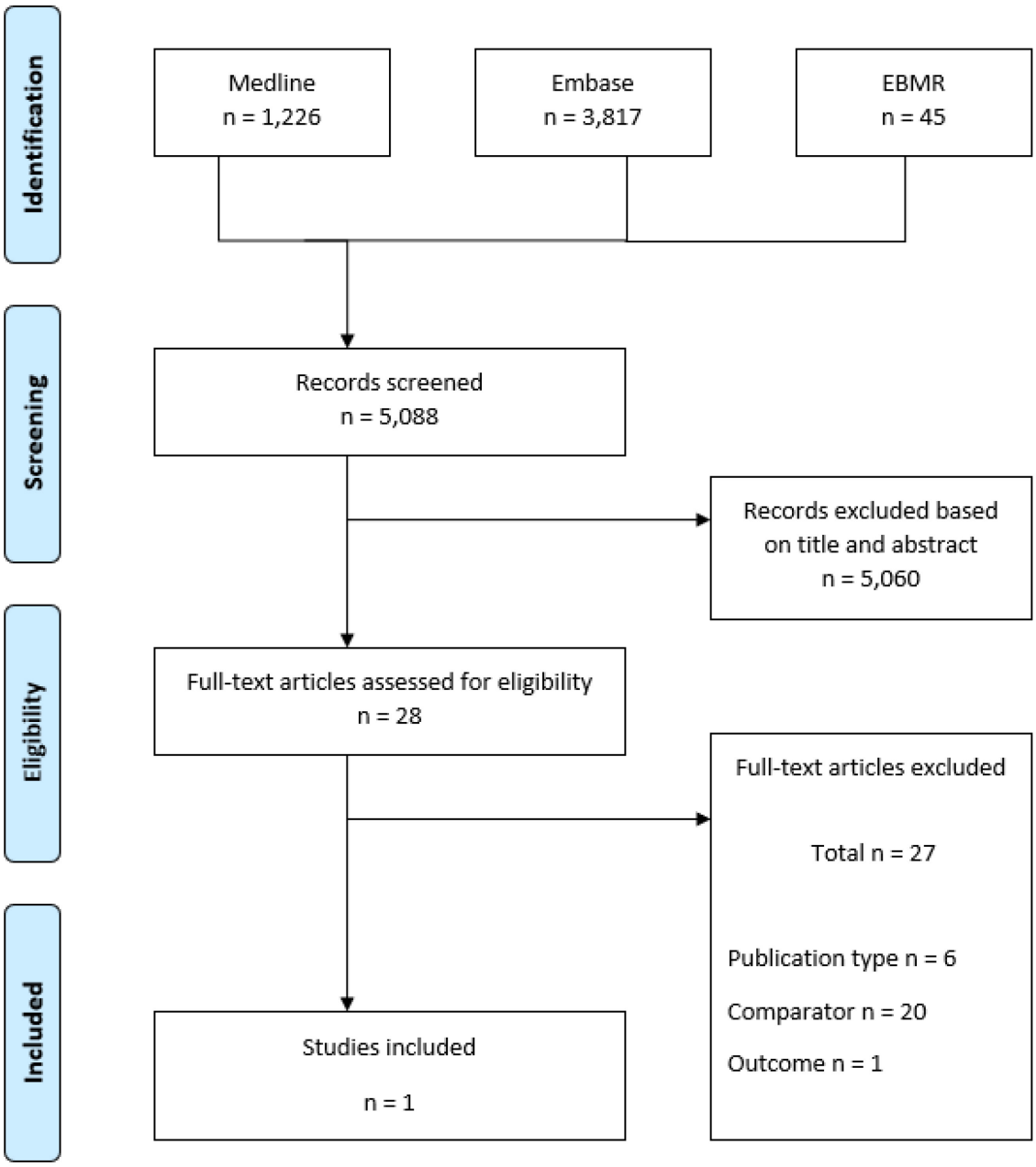
The costs, budget impact, and cost-effectiveness searches resulted in 5,088 unique records (Medline: 1,226 records; Embase: 3,817 records; EBMR: 45 records). In total, 5,060 records were excluded by title abstract screening, resulting in 28 full-text articles to be assessed for eligibility. No additional literature was found by hand search. In total, 27 full-text articles were excluded based on no full-text availability (n=6), no comparator of interest (n=20), and no outcome of interest (n=1).

One study assessed the cost-effectiveness of monthly zoledronate, 3-monthly zoledronate, and monthly denosumab in women with BC and BM and was therefore included (Shapiro 2017).[88] Study characteristics are shown in Table 23.

No additional studies or systematic reviews were identified by hand searching the reference lists. The PRISMA flow diagram is shown in Figure 27.

8.2.1 PRISMA flow diagram

Figure 27. PRISMA flowchart of the costs, cost-effectiveness, and budget impact of the systematic literature search



Key: EBMR – Evidence-Based Medicine Reviews.

8.2.2 Evidence table

Table 23. Economic study: study characteristics

Author/affiliation	Charles L. Shapiro, Icahn School of Medicine, Mt Sinai, NY; James P. Moriarty, Paul J. Novotny, and Bijan J. Borah, Mayo Clinic Cancer Center; Paul J. Novotny, Mayo Clinic, Rochester, MN; Stacie Dusetzina, University of North Carolina at Chapel Hill, Chapel Hill, NC; Andrew L. Himelstein, Helen F. Graham Cancer Center and Research Institute; Stephen S. Grubbs, Christiana Care NCI Community Oncology Research Program, Newark, DE; and Jared C. Foster, University of Michigan, Grand Rapids, MI
Title	Cost-effectiveness analysis of monthly zoledronic acid, zoledronic acid every 3 months, and monthly denosumab in women with breast cancer and skeletal metastases: CALGB 70604 (alliance)
Year of publication	2017
Publication source	Journal of Clinical Oncology
Study design	Cost-effectiveness study
Sample size and population	Hypothetical cohort of 10,000 women with breast cancer and bone metastases for SRE prevention
Intervention	Monthly zoledronate
Comparator	3-monthly zoledronate and monthly denosumab
Outcomes	Mean costs, mean SREs, QALY year 1, QALY year 2, cost per SRE avoided with monthly ZA, and ZA every 3 months as reference
Country, perspective	US payer's perspective
Time horizon	A 2-year time horizon was used
Discount rates	Future costs are discounted at an annual rate of 3%
Clinical parameters	For annual probabilities of first SREs and subsequent SREs associated with denosumab from Xie et al[99] (referring to Stopeck et al.[100]) and for monthly ZA and ZA every 3 months from NCT00869206[77]
Cost parameters	Drug costs; administration costs; costs associated with having an SRE, bone surgery, pathologic fracture, spinal cord compression, radiation to bone
Sources	Monthly probabilities, utilities, and costs from published literature and Centers for Medicare & Medicaid Services reimbursement rates
Main cost-effectiveness findings	ZA every 3 months is dominant and denosumab is dominated
Key: SRE – skeletal-related event; QALY– quality-adjusted life-year; US – United States; ZA – zoledronate.	

8.2.3 Findings from the literature search

One cost-effectiveness study (Shapiro 2017)[88] was identified after the full-text screening as described in Section 8.2. The authors assessed the cost-effectiveness of monthly zoledronate, 3-monthly zoledronate, and monthly denosumab in women with BC and skeletal metastases. A Markov model was used to assess the cost-effectiveness of monthly zoledronate vs 3-monthly zoledronate and monthly denosumab. The model consisted of 11 distinct health states starting with patients with no SREs and no history of SREs. Patients could move from the first state to SRE status (no SRE, first on-study SRE, subsequent SRE, no SRE but history of SRE) and from SRE status to SRE type (pathologic fracture, radiation to the bone, surgery to the bone, spinal cord compression) and finally to the death state.

The cost-effectiveness analysis was conducted from the US payer's perspective using a 2-year time horizon. Monthly probabilities, utilities, and costs came from published literature and Centers for Medicare & Medicaid Services reimbursement rates. Included cost parameters were drug costs, administration costs, and costs associated with having an SRE, bone surgery, pathologic fracture, spinal cord compression, and radiation to bone. All costs before 2015 were inflated to 2015 US dollars. Future costs were discounted by an annual rate of 3%. Costs of the death state were not counted due to similar mortality among the 3 treatment groups. Sensitivity analyses were conducted to estimate the results of different scenarios using different SRE probabilities for denosumab and zoledronate.

Monthly zoledronate vs 3-monthly zoledronate treatment resulted in 0.90 and 0.91 QALYs in year 1 and 0.91 and 0.91 QALYs in year 2, respectively. The effectiveness comparing 3-monthly vs monthly treatment was considered the same. Mean costs counted for drug costs, administration costs, and costs of SREs. Mean zoledronate costs in 2015 United States dollars (USD) were 5,667 USD and 9,290 USD for monthly and 3-monthly zoledronate treatment, respectively. Findings could not be transferred to the Swiss context due to significant differences in unit costs and limitations of the study (see Appendix 8 for quality assessment).

8.2.4 Findings costs

Question 3: What are the costs of BTA use?

Drug costs were sourced from the Spezialitätenliste[46] and sales data of the Sasis data pool[93], whereas administration costs were calculated based on the TARMED catalogue[94] as described in Section 8.1.4. Table 24 shows the inputs used to calculate the annual drug costs for each treatment arm. The public calculated mean price per unit is 149.36 CHF for zoledronate and 478.05 CHF for denosumab (Xgeva). Zoledronate infusion costs are 112.81 CHF per infusion and for denosumab are 41.15 CHF per injection (Table 25)[95].

Table 24. Drug costs

Treatment	Dosage per SmPC[23 28]	Price per dose[46] (public price)
Zoledronate based on weighted average of sales data (for details see table below)[a]	Intravenously every 3–4 weeks, 4 mg infusion over at least 15–20 minutes	149.36 CHF[a]
Denosumab, Xgeva	Subcutaneously every 4 weeks, 120 mg / 1.7 mL	478.05 CHF
[a] Based on Sasis COGE data pool, sales data 2019.[93] Key: CHF – Swiss franc		

Zoledronate drug	Sales[93]	Price per dose (public price)[46]
Zoledronat Fresenius Onco	1,934	129.45 CHF
Zoledronat Onco Labatec	2,574	140.75 CHF
Zometa	2,113	206.75 CHF
Zoledronsäure Onco Sandoz	5,622	140.75 CHF
Zoledronat Teva onco	1,411	140.75 CHF
Key: CHF – Swiss franc.		

Table 25. Drug administration costs

Treatment	Resource use	TARMED codes	AL (in TP)	TL (in TP)	Costs using national weighted average TPW
Zoledronate	Assuming 10 min consultation and 30 min chair time / monitoring	0.0010 0.0030 2 x 0.137 0.0855	10.42 5.21 4.17 0	8.19 4.1 28.01 35.29	112.81 CHF
Denosumab	Assuming a 15 min GP visit	0.0010 0.0020 0.0030	10.42 10.42 5.21	8.19 8.19 4.1	41.15 CHF
Source: FOPH, HTA report 2020[95] Key: AL – Medical performance; CHF – Swiss Franc; GP – general practitioner; TL – technical performance; TP – Taxpunkt; TPW – Taxpunktwert.					

SRE costs were based on a cost study by Lothgren et al.[97] Monthly SRE probabilities and SRE costs are shown in Table 26 and Table 27.

Table 26. Probabilities of experiencing a skeletal-related event

Skeletal-related event probabilities	Zoledronate[101]	Denosumab[101]
Radiation to bone	0.0077	0.0059
Pathological fracture	0.0092	0.0077
Surgery to bone	0.0005	0.0004
Spinal cord compression	0.0009	0.0009

Table 27. Costs of skeletal-related events

Skeletal-related event costs	Euro 2012[97 98]	CHF 2012[97 98]	CHF 2020[97 98]
Pathologic fracture	25,987 EUR	31,184 CHF	29,638 CHF
Radiation to bone	13,407 EUR	16,088 CHF	15,290 CHF
Surgery to bone	49,330 EUR	59,196 CHF	56,260 CHF
Spinal cord compression	51,188 EUR	61,425 CHF	58,379 CHF
Key: CHF – Swiss franc; EUR – Euro.			

The monthly cost of BTAs including administration costs (for 4-weekly zoledronate and 3.5-weekly denosumab) ranges from 262.17 CHF to 519.20 CHF, and the cost of treating an SRE ranges from 29,638 CHF to 58,379 CHF.

8.2.5 Findings for budget impact

Question 4: What is the budget impact of the 3-monthly use of BTAs vs monthly use?

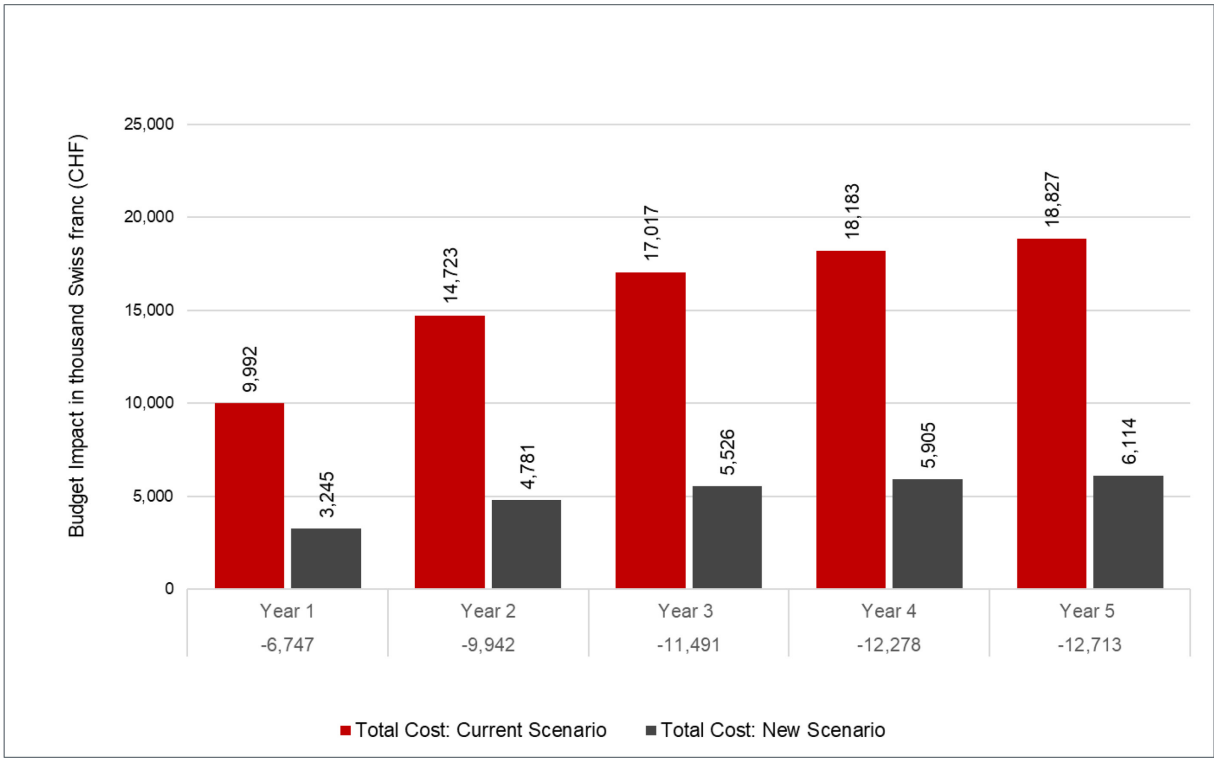
The budget impact model output represents the total current incident population of 2,497 patients with BM on BTA treatment with an annual patient growth of 1.01%. The total number of patients over 5 years is 15,365.

Budget impact for 3-monthly treatment compared to monthly treatment resulted in a decrease in costs of CHF 6,747,073 in year 1 and a total decrease in costs of CHF 53,170,447 over the 5-year time horizon. The first year of treatment is more expensive compared to years 2 to 5 because more patients will be on treatment (i.e., treatment discontinuation is lower). Therefore, cost savings are the highest in year 1. Budget impact annual and total BTA treatment costs over the 5-year time horizon are presented in Table 28 and Figure 28.

Table 28. Annual and cumulative budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (5 years)
Total cost: Monthly BTA treatment	CHF 9,992,031	CHF 14,722,952	CHF 17,017,054	CHF 18,183,040	CHF 18,827,330	CHF 78,742,407
Total cost: 3-monthly BTA treatment	CHF 3,244,958	CHF 4,781,347	CHF 5,526,367	CHF 5,905,026	CHF 6,144,262	CHF 25,571,960
Budget impact	CHF −6,747,073	CHF −9,941,605	CHF −11,490,688	CHF −12,278,014	CHF −12,713,068	CHF −53,170,447
Key: CHF – Swiss franc.						

Figure 28. Budget impact of the 3-monthly and monthly treatment



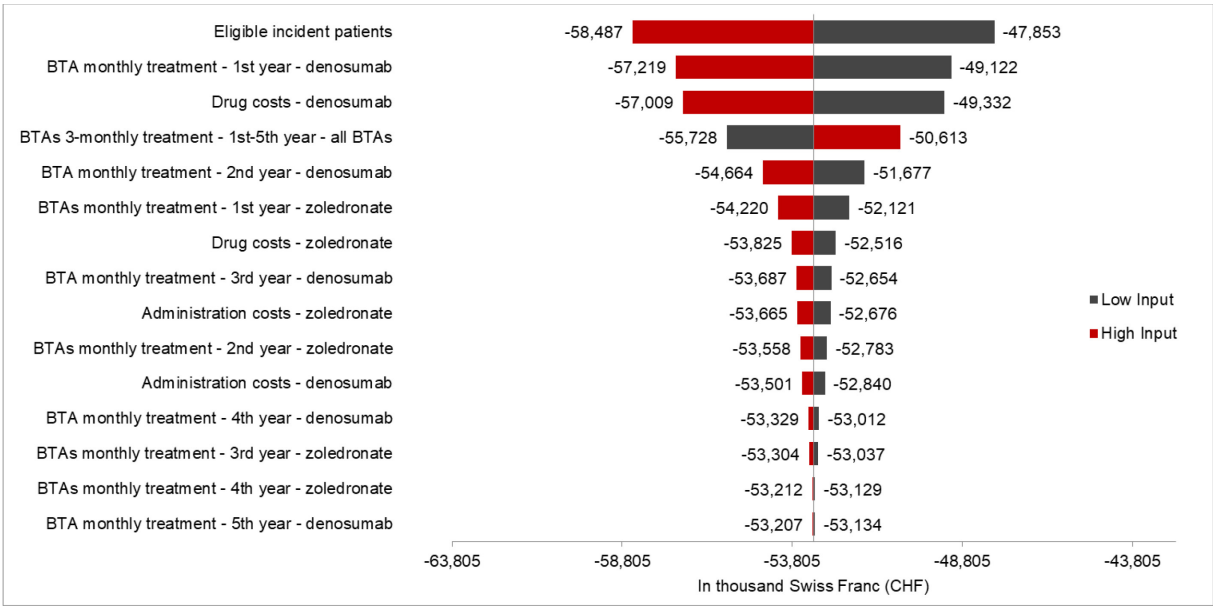
Key: CHF – Swiss franc.

Sensitivity analyses of the budget impact

One-way sensitivity analyses were conducted to test the sensitivity of the model to variation in the model parameters by varying the key model parameters over a range of ±10% of the base case value. The output of the one-way sensitivity analyses is the total budget impact over the 5-year time horizon with a base case value of CHF −53,170,447. The total budget impact results are shown in Figure 29. The width of the bars represents the variation in the budget impact over the range of tested parameter values.

The budget impact analysis results were most sensitive to (1) the number of eligible incident patients, (2) first-year denosumab dosing of the monthly treatment arm, and (3) the drug costs of denosumab. The sensitivity analysis showed a maximum expected budget impact of CHF −58,487,492 when eligible incident patients of the current year were increased by 10% and a minimum expected budget impact of CHF −47,853,403 when incident patients of the current year were decreased by 10%.

Figure 29. Univariate sensitivity analysis of the budget impact



Key: BTA – bone-targeting agent; CHF – Swiss franc.

Dosing

Base case analyses compared 3-monthly zoledronate or denosumab treatment to those patients treated monthly (i.e., 3- to 4-weekly treatment per the SmPC). For the scenario analysis, a reduced dosing frequency was used for the monthly treatment arm, as described in the cross-sectional survey study by Mark et al.[18] Scenario analyses assumed that 3.49% of patients will start with 3-monthly treatment and an additional 8.14% of patients will start 3-monthly treatment after 3 months. After 1 and 2 years, an additional of 16.28% and 33.72% of patients were assumed to be on 3-monthly treatment, respectively. After year 3 and year 4, 3-monthly treatment percentages were assumed to be the same as after year 2. Dose interval adjustment after initiating 3-monthly BTA treatment was not counted, as supporting data were not available.

For the base case analyses, 100% of patients were assumed to be on monthly treatment per the SmPC[23] [28] (zoledronate median dosage of 3.5 weeks and denosumab dosage of every 4 weeks). Using data from the survey study of Mark et al.[18] resulted in a difference of CHF 661,402 in year 1 and CHF 7,110,143 over the 5-year time horizon. Base case 3-monthly BTA treatment resulted in a greater cost decrease compared to the scenario results, as monthly patients receive less drug in the scenario analysis. Budget impact dosing results are shown in Table 29.

Table 29. Annual and cumulative budget impact of different dosing frequencies

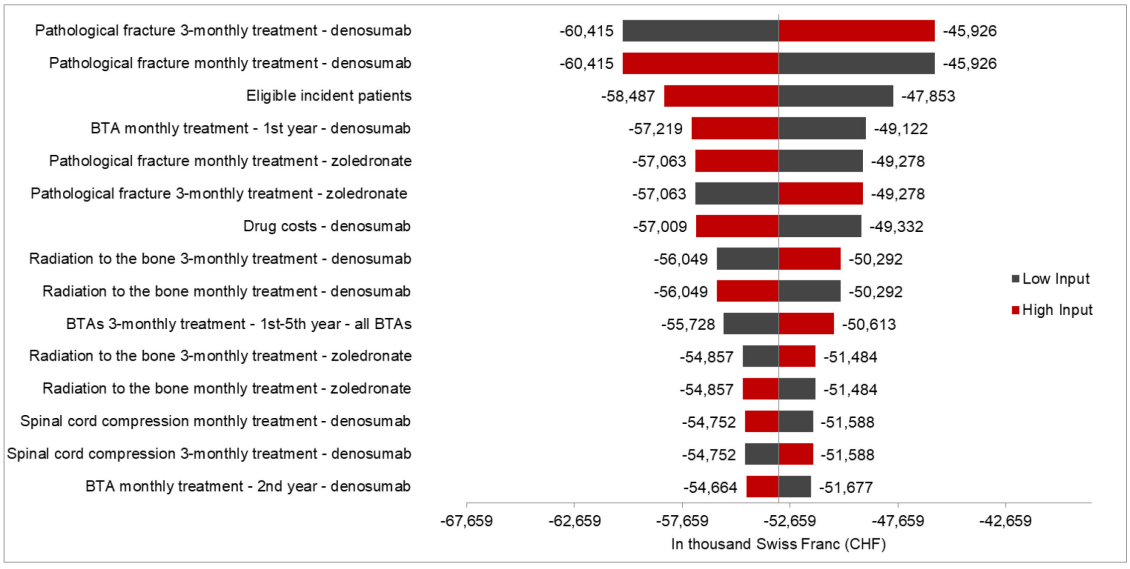
	Year 1	Year 2	Year 3	Year 4	Year 5	Total (5 years)
Budget impact base case results	CHF −6,747,073	CHF −9,941,605	CHF −11,490,688	CHF −12,278,014	CHF −12,713,068	CHF −53,170,447
Budget impact scenario results	CHF −6,085,671	CHF −8,401,043	CHF −9,041,779	CHF −9,390,682	CHF −9,604,882	CHF −42,524,056
Difference	CHF 661,402	CHF 1,034,088	CHF 1,449,116	CHF 1,877,442	CHF 2,088,095	CHF 7,110,143
Key: CHF – Swiss franc.						

SRE costs

Budget impact one-way sensitivity analyses including SREs were conducted to test the sensitivity of the model to variation in the model parameters by varying the key model parameters over a range of ±10% of the base case value. SRE costs were not included in the base case analysis as the meta-analysis did not show a significant difference between the 3-monthly and monthly dosing interval.

The budget impact 5-year time horizon base case value was CHF −53,170,447. Budget impact analysis results were most sensitive to (1) annual denosumab probability of a pathological fracture of the 3-monthly treatment arm, (2) annual probability of a denosumab pathological fracture of the monthly treatment arm, and (3) eligible incident patients. The sensitivity analysis showed a maximum expected budget impact of CHF −60,414,725 when annual probability of a denosumab pathological fracture for the 3-monthly BTA treatment scenario percentage was decreased by 10% and a minimum expected budget impact of CHF −45,926,170 when the annual probability of a denosumab pathological fracture of the monthly BTA treatment scenario was increased by 10%. One-way sensitivity analyses for SRE results are shown in Figure 30.

Figure 30. Univariate sensitivity analysis of skeletal-related event costs



Key: BTA – bone-targeting agent; CHF – Swiss franc.

8.2.6 Findings for cost-effectiveness

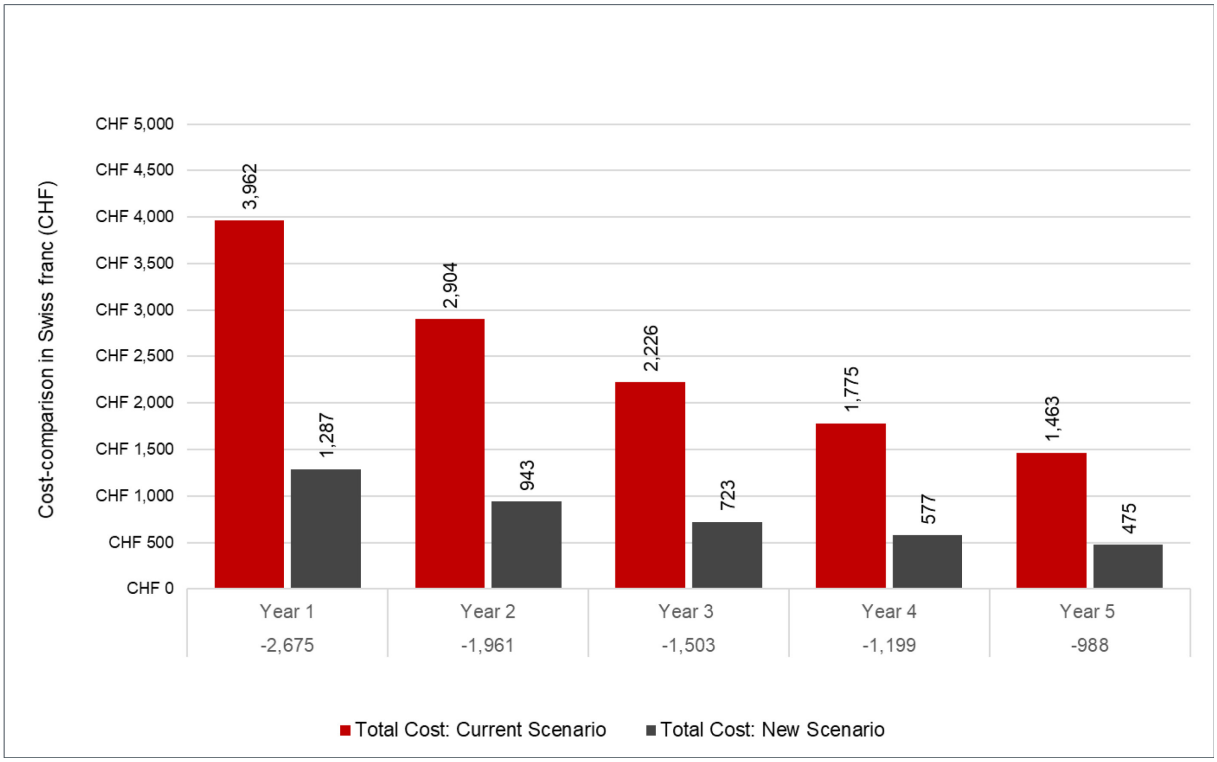
Question 5: How cost-effective is the less frequent use of BTAs?

Cost-comparison of 3-monthly BTA treatment and monthly BTA treatment resulted in an incremental cost decrease of CHF 2,675 per patient in year 1 and a total incremental decrease in cost of CHF 8,326 per patient over the 5-year time horizon. The cost comparison per average patient for zoledronate, denosumab, and the combined BTA treatment results (based on market shares) over the 5-year time horizon is presented in Table 30. Figure 31 shows the cost comparison per average patient for the combined BTA treatment results (based on market shares) over 5-years of treatment.

Table 30. Annual and cumulative cost comparison

Treatment costs (per treated patient)	**First year of treatment**	**Second year of treatment**	**Third year of treatment**	**Fourth year of treatment**	**Fifth year of treatment**	**Total (5 years)**
Total cost: *Monthly zoledronate*	CHF 2,631	CHF 1,929	CHF 1,479	CHF 1,179	CHF 972	CHF 8,189
Total cost: *3-monthly zoledronate*	CHF 767	CHF 563	CHF 431	CHF 344	CHF 283	CHF 2,389
Difference	CHF −1,864	CHF −1,366	CHF −1,047	CHF −835	CHF −688	CHF −5,801
Total cost: *Monthly denosumab*	CHF 4,559	CHF 3,342	CHF 2,562	CHF 2,043	CHF 1,684	CHF 14,191
Total cost: *3-monthly denosumab*	CHF 1,520	CHF 1,114	CHF 854	CHF 681	CHF 561	CHF 4,730
Difference	CHF −3,040	CHF −2,228	CHF −1,708	CHF -1,362	CHF −1,123	CHF −9,460
Total cost: *Monthly BTA*	CHF 3,962	CHF 2,904	CHF 2,226	CHF 1,775	CHF 1,463	CHF 12,330
Total cost: *3-monthly BTA*	CHF 1,287	CHF 943	CHF 723	CHF 577	CHF 475	CHF 4,004
Difference	CHF −2,675	CHF −1,961	CHF −1,503	CHF −1,199	CHF −988	CHF −8,326
Key: BTA – bone-targeting agent; CHF – Swiss franc.						

Figure 31. Difference in cost of the 3-monthly and the monthly treatment

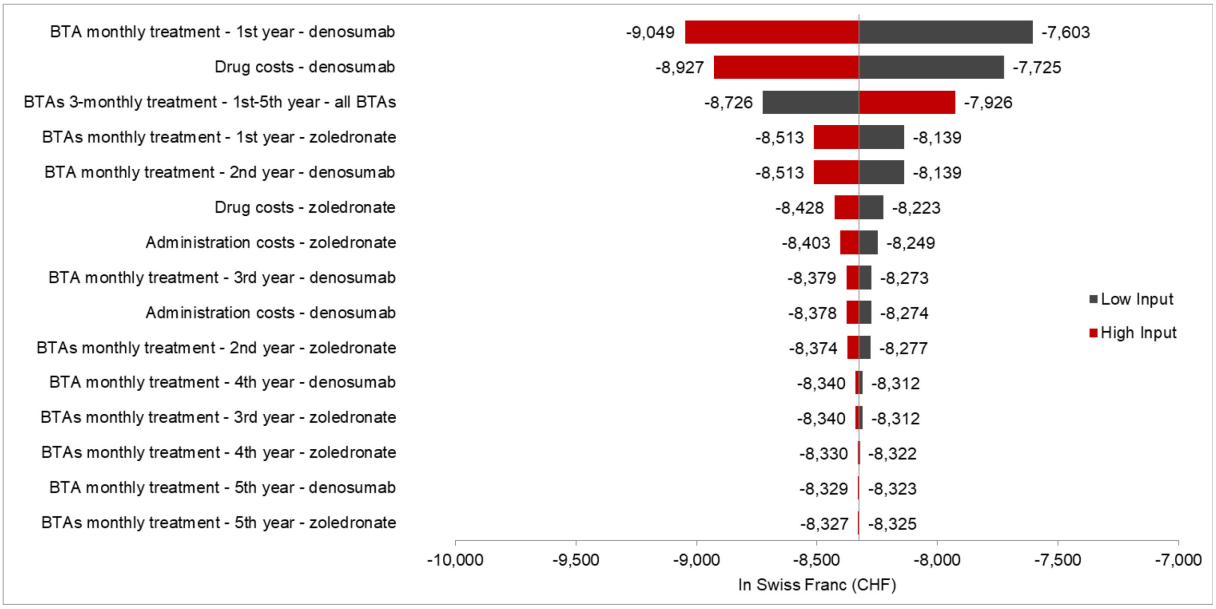


Sensitivity analysis of the cost comparison

One-way sensitivity analyses were conducted to test the sensitivity of the model to variation in the model parameters by varying the key model parameters over a range of ±10% of the base case value. The output of the one-way sensitivity analyses is the total direct cost (cost comparison) per patient over the 5-year time horizon, with a base case value of CHF −8,326. The total cost-comparison results are shown in Figure 32.

The cost-comparison analysis results were most sensitive to (1) first-year denosumab dosing of the monthly treatment arm, (2) drug costs of denosumab, and (3) zoledronate and denosumab dosing of the 3-monthly treatment arm. The sensitivity analysis showed a maximum expected cost decrease per patient of CHF 9,049 when denosumab drug cost was increased by 10% and a minimum expected cost decrease per patient of CHF 7,603 when first-year denosumab drug cost was decreased by 10%.

Figure 32. Univariate sensitivity analysis of the cost-comparison analysis



Key: BTA – bone-targeting agent; CHF – Swiss franc.

Limitations

Some of the parameters relevant for the model were not described in the literature and could not be attained otherwise. Therefore, assumptions were made for these parameters, including the size of the target population, GP and nurse administration time, dosing, treatment discontinuation, and SRE probabilities and costs. While a deliberate effort has been made to employ methodologically sound modelling techniques, the inputs and assumptions used in this model may not align with the whole population served by the Swiss payer. The following limitations are noted:

i) The incidence was calculated from data based on multiple sources, and some of these sources may not match the population of Switzerland.

ii) To calculate the incidence, mortality was used as a proxy for metastatic disease.

iii) GP and nurse time to administer an infusion or SC injection may be different depending on patient and/or GP and nurse.

iv) The base case analysis assumed monthly (i.e., 3- to 4-weekly treatment per the SmPC over a 5-year time horizon). SmPC dosing frequency may not match the dosing received by the patient, which was shown in a cross-sectional survey study where the dosing was reduced over time.[18]

v) SRE costs in 2012 Euros were converted to 2020 CHF by using exchange and inflation rates, which may deviate from the current SRE treatment cost.

Summary statement for costs, cost-effectiveness, and budget impact

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Based on the health economic literature search, only 1 study assessed the cost-effectiveness of zoledronate every month, zoledronate every 3 months, and denosumab every month. According to this study, the effectiveness of 3-monthly vs monthly treatment could be considered the same, corresponding with the efficacy findings of the meta-analyses. Mean costs of monthly treatment with zoledronate were higher compared to 3-monthly treatment. Effectiveness and costs were not assessed for denosumab 3-monthly vs denosumab monthly treatments. These findings are in line with the findings of the performed budget impact analyses, where the introduction of 3-monthly treatment for patients with BM results in a budget impact decrease in the base case.

The annual budget impact decrease in costs was CHF 6,747,073 in year 1 up to CHF 12,713,068 in year 5 and CHF 53,170,447 over the 5-year time horizon.

The cost-comparison model showed a cost decrease of CHF 2,675 and CHF 988 per patient in years 1 and 5, respectively, with a total decrease in costs of CHF 8,326 per patient over the 5-year time horizon. Sensitivity analyses showed the budget impact analysis results were most sensitive to (1) the number of eligible incident patients, (2) first-year denosumab dosing of the monthly treatment arm, and (3) the drug costs of denosumab. Cost-comparison results were most sensitive to (1) first-year denosumab dosing of the monthly treatment arm, (2) drug costs of denosumab, and (3) zoledronate and denosumab dosing of the 3-monthly treatment arm.

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9 Legal, social, and ethical issues

9.1 Methodology for legal, social, and ethical issues

9.1.1 Databases and search strategy

The database search for evidence on legal, social, and ethical issues was conducted together with the search for clinical evidence as described in Section 7.1.1.

9.1.2 Other sources

In addition to the search in databases via OVID, a hand search for literature on legal, social, and ethical issues was performed as described in Section 7.1.2.

Relevant literature regarding the legal section of this report was further obtained through a search on the Swiss legislation database. As search terms, names of the drugs (zoledronate, ibandronate, and denosumab) were entered into the database.

9.1.3 Assessment of quality of evidence

There were no relevant articles identified that could help answer the research question (Figure 33).

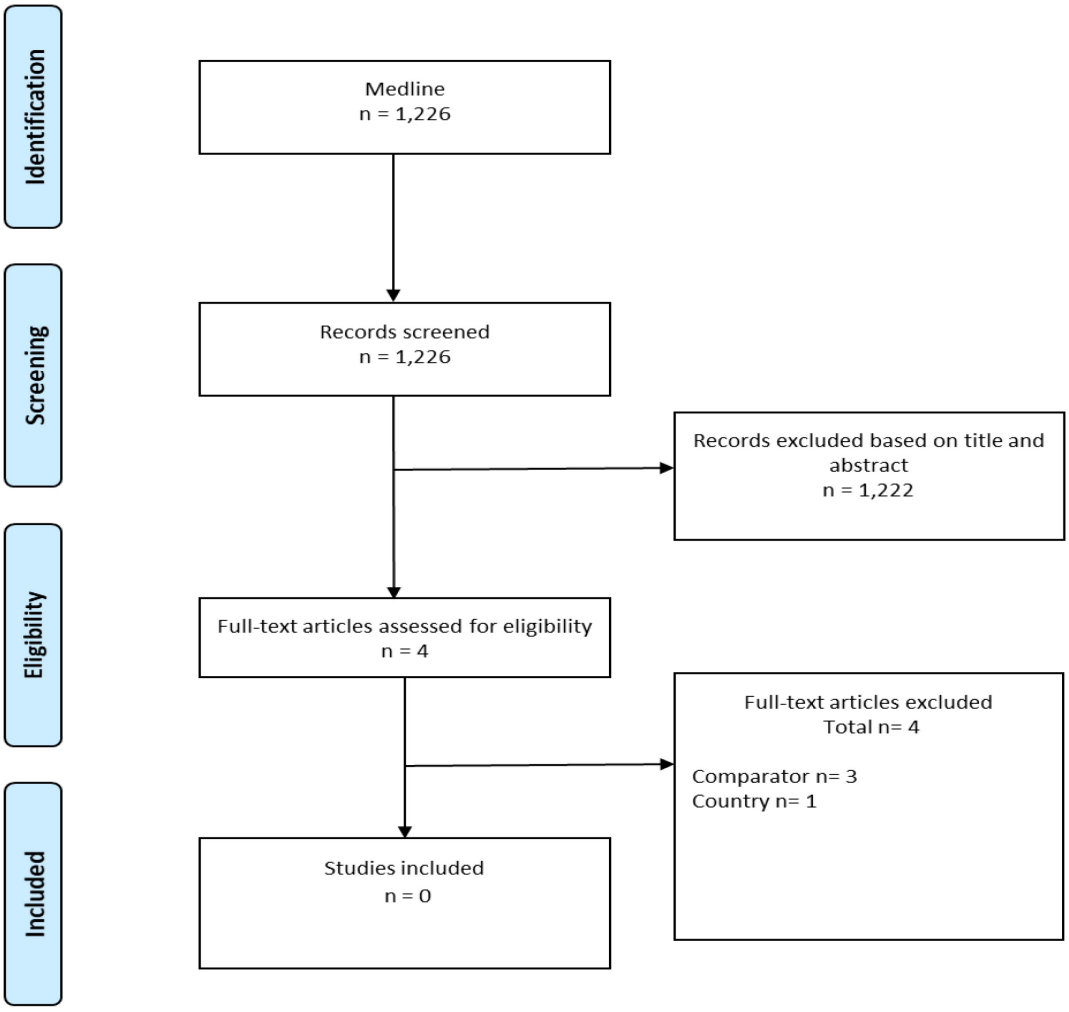
9.1.4 Methodology data analysis for legal, social, and ethical issues

No data analysis was performed, as there were no relevant publications identified during the literature search.

9.2 Results for legal, social, and ethical issues

9.2.1 PRISMA flow diagram

Figure 33. PRISMA flowchart of the legal, social, and ethical issues of the systematic literature search



9.2.2 Evidence table

There were no relevant articles identified during the literature search.

9.2.3 Findings for legal issues

There were no relevant articles identified that could help answer the research question regarding legal issues related to the less frequent administration of BTAs.

9.2.4 Findings for social issues

There were no relevant articles identified that could help answer the research question regarding social issues related to the less frequent administration of BTAs

9.2.5 Findings for ethical issues

There were no relevant articles identified that could help answer the research question regarding ethical issues related to the less frequent administration of BTAs.

Summary statement for legal, social, and ethical issues

There was no available evidence found to help answer the research question regarding legal, social, and ethical issues.

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10 Organisational issues

10.1 Methodology for organisational issues

10.1.1 Databases and search strategy

The databases search for evidence on organisational issues was conducted together with the search for clinical evidence as described in Section 7.1.1.

10.1.2 Other sources

In addition to the search in databases via OVID, a hand search for literature on organisational issues was performed as described in Section 7.1.2.

10.1.3 Assessment of quality of evidence

There were no relevant articles identified that could help answer the research question (Figure 34).

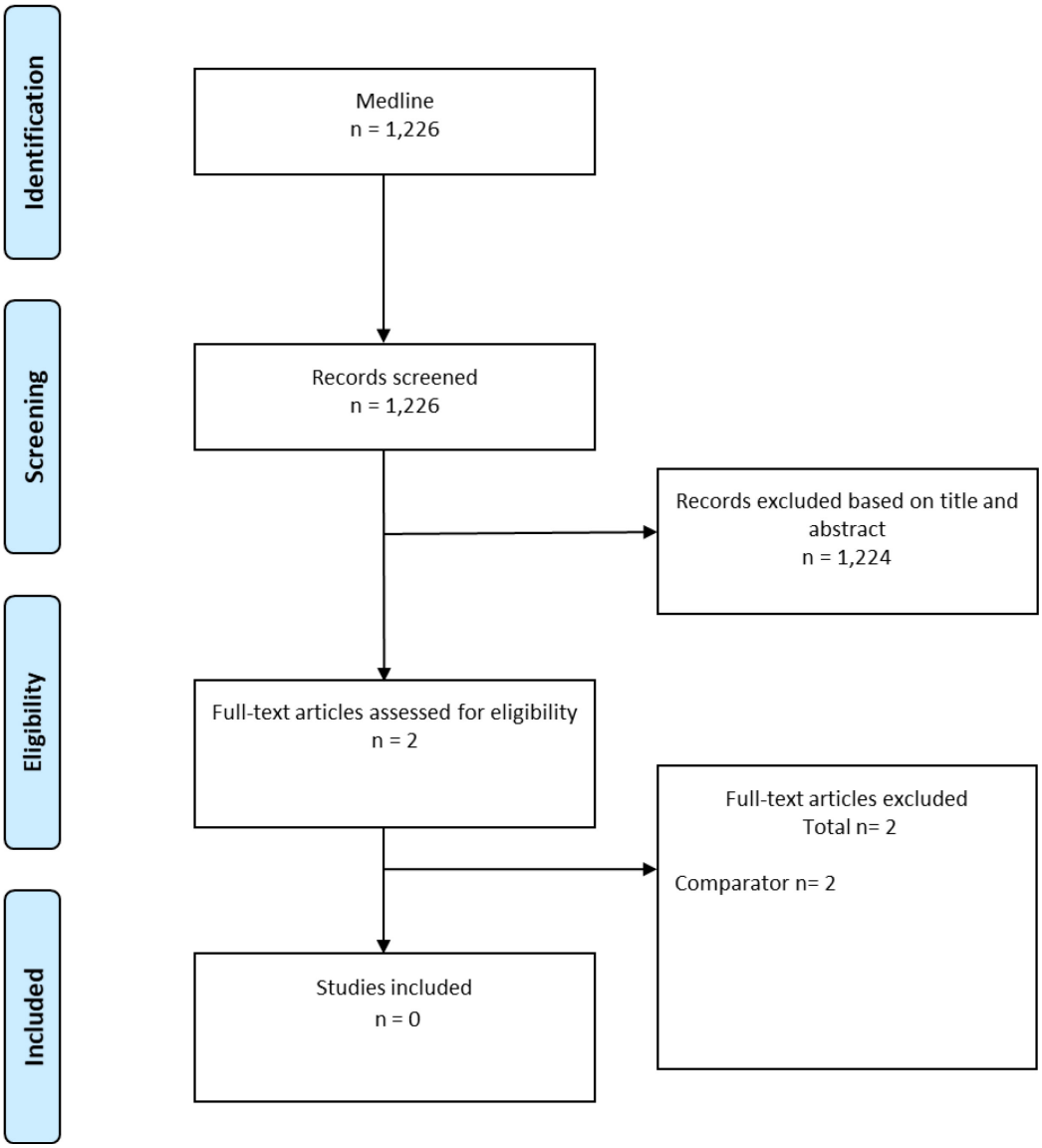
10.1.4 Methodology for data analysis for organisational issues

No data analysis was performed, as there were no relevant publications identified during the literature search.

10.2 Results for organisational issues

10.2.1 PRISMA flow diagram

Figure 34. PRISMA flowchart of the organisational issues of the systematic literature search



10.2.2 Evidence table

There were no relevant articles identified during the literature search.

10.2.3 Findings for organisational issues

There were no relevant articles identified that could help answer the research question regarding organisational issues related to the less frequent administration of BTAs.

Summary statement for organisational issues

There was no available evidence found to help answer the research question regarding organisational issues.

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11 Additional issues

In the case that the 3-monthly administration of BTAs in cancer patients with bone metastases is noninferior to monthly administration, a number of other topics need to be considered. Clinical guidelines discuss the possibility of extended dosing intervals for BTAs due to improvement in survival of patients and thus longer treatment times and currently published evidence. However, due to the limitations of the available clinical evidence also mentioned in this report, no clear recommendation is given on the de-escalation of BTA administration[19 102,103].

In the real-world setting, it seems to be the case that patients are treated for 1 to 2 years with BTAs every month before the administration pattern is switched to administration every 3 months.[18] It is not clear what effect switching to 3-monthly dosing has on this analysis.

As described in Section 3, bone metabolism markers can provide insights into the interaction of tumour and bone so that changes in these markers can be seen as surrogates for SREs before they occur. The role of these markers in the treatment of BM is under discussion as an aid to guide the decision of whether or not to extend the dosing interval of BTAs before SREs eventually occur. Guidelines advise against longer dosing intervals of BTAs when bone resorption markers are elevated. However, there is no clear guideline on how to incorporate the measurement of bone markers into the treatment of BM for routine practice[19 102,103].

Monitoring bone marker concentrations may be of special interest when denosumab dosing is reduced to 3-monthly administration, since denosumab discontinuation was found to be associated with a rapid increase in bone markers possibly resulting in a rise in vertebral fractures (rebound effect of denosumab)[35 104].

Finally, the introduction of biosimilars is an emerging development in market trends. Patents for denosumab are starting to expire and the entry of biosimilar competitors is highly likely in the next few years.[105-107]

12 Discussion

For this report, 7 RCTs and 2 non-RCTs involving 3,682 patients were identified from the systematic search as evidence for investigating the efficacy and safety of the use of BTAs with different administration frequencies in cancer patients with BM. 5 of the included studies investigate IV zoledronate and 4 of them SC denosumab. No evidence was found for IV ibandronate. 5 of the RCTs were open-label studies, while the remaining 2 were blinded. The included RCTs varied widely regarding sample size (n=18–1,822).

3 of the included studies were noninferiority studies, with all of them investigating zoledronate dosing. All of them found 3-monthly dosing to be noninferior to monthly dosing. Amadori 2013 reports the noninferiority margin for SMR whilst Himelstein 2017 and Hortobagyi 2017 report their margin for SRE absolute risk rates. Neither Amadori 2013 nor Hortobagyi 2017 justify their chosen margin. Himelstein 2017 justifies the margin by reference to 4 other studies investigating the treatment effect of zoledronate vs placebo in different cancer types. As the predefined margins differ, are based on absolute risk and there seems to be no clinical consensus around a noninferiority margin for the outcome of interest, this complicates the interpretation of the results of the meta-analysis in terms of noninferiority; thus, it is not possible to state with confidence whether 3-monthly administration is noninferior to monthly administration of BTAs based on this analysis. However, after conversion of the noninferiority margins from the Himelstein and Hortobagyi trials, the comparison suggested a noninferiority for the primary outcome SRE.

In all trials, both the risk of SREs as the acknowledged efficacy parameter in the indication and the incidence of AEs for safety evaluation were investigated. SREs were defined as fracture, spinal cord compression, radiation to bone, and surgery involving bone in all but one study, where surgery to bone was omitted. The definition of fracture varied, but it is assumed to be clinically insignificant. The definition of RAEs differed widely across studies.

Data on QoL, pain score, and biomarkers were limited or reported inconsistently so that they could not be analysed further. However, 1 study reporting on QoL did not find a statistically significant difference in the physical subdomain score of the EORTC-QLQ-C30 between the different dosing schedules for zoledronate and denosumab.[83] Data on changes in biomarkers that reported for zoledronate[1 77] and denosumab[84 85] by 2 studies each, including serum or urine NTx and CTx, indicate that there may be a significant increase in biomarker levels in the 3-monthly dosing regimen. However, these findings need to be confirmed and the clinical relevance assessed.

In general, the overall body of evidence for the meta-analysis was judged to be of moderate or low risk of bias. The heterogeneity between study outcomes reported in the trials was assumed to be low. Cases

of heterogeneity in outcomes between studies can be explained by differences in definition of these outcomes. CIs were wide in some cases, suggesting that studies may not be adequately powered for these endpoints.

In the meta-analyses, between-study heterogeneity was found to be consistently low with 1 exception, where I^2 reached a value of 63%. For the interpretation of heterogeneity, a commonly used rule from 2002 was applied[67]. For the context of meta-analyses of RCTs, different thresholds for the interpretation of heterogeneity are presented in the Cochrane Handbook for Systematic Reviews of Interventions[108]. However, applying these thresholds does not have an impact on the interpretation from our study that between-study heterogeneity was generally low (Cochrane: “might not be important”), with the one exception where heterogeneity was judged as moderate to substantial.

The results from the meta-analyses applying the RE model showed no statistically significant effect between both dosing regimens for SREs, AEs, or SAEs. The result for SREs was RR: 1.01; 95% CI: 0.82, 1.24 with the RE model and RR: 0.99; 95% CI: 0.87, 1.12 with the FE model. These results indicate SREs may decrease by up to 18% or increase by 24% when 3-monthly dosing is compared to monthly dosing. Heterogeneity was low (I^2=0%). The RR result for AEs was RE: RR: 0.97; 95% CI: 0.93, 1.02 in the main analyses. However, the CI of the FE model indicates a marginally statistically significant difference favouring the 3-monthly administration (FE: RR: 0.97; 95% CI: 0.94, 0.99) (prediction interval: 0.86, 1.09) (Figure 8). The results suggest that 3-monthly use of BTAs may lead to a reduction in AEs up to 7% or an increase up to 2%. Heterogeneity between the studies was low (I^2=0%). The results indicated no difference in SAEs and AEs of special interest in this indication, like hypocalcaemia, ONJ, or RAEs. The SAE RE model CIs showed a potential decreased risk of 21% vs a potential increased risk of 9% (Figure 11).

Sensitivity analyses assessing the single BTAs separately and including non-RCTs confirmed the results from the main analyses. When subtypes of SREs were assessed separately, differences in risk of clinical fractures and surgery to bone were found to be statistically significant when treated with zoledronate. However, results were not confirmed in pooled analyses, indicating that the risk of different SRE subtypes may vary between different BTAs. When applying the FE model, difference in risk of AEs and RAEs was found to be marginally statistically significant between the treatment groups favouring the 3-monthly administration of BTAs.

Thus, a 3-monthly administration may lead to a benefit in reducing SAEs by up to 21% while increasing SREs by up to 24% or it may decrease SRE risk by 18% whilst increasing SAE risk by 9%. Varying CIs complicate the interpretation of the results. The analysis suggests that de-escalating BTAs does not reduce the effect on SREs or increase side effects, which in turn suggests that monthly dosing of BTAs

may be in effect overdosing patients. The real-world practice of switching to 3-monthly dosing adds weight to this argument.

The findings of this report are similar to the findings of other systematic reviews investigating the extension of BTA dosing intervals in cancer patients[40 41 70 71 74 109]. Notably, Santini et al. 2019[73] found a statistically significant difference favouring the 3-monthly schedule of zoledronate in terms of AEs (RR: 1.17; 95% CI: 1.06, 1.29), while this report found only a numerical difference in the main analysis. The reason might be differences in event definitions. One identified systematic review from 2013[110] did not perform a meta-analysis due to major differences between the identified trials. Most of the trials included in this HTA report were published after the time of the mentioned review.

To estimate the impact and costs of the different dosing schedules, a de novo budget impact model and cost-comparison model were developed. The results indicate that the introduction of 3-monthly treatment for patients with bone metastases in Switzerland might be associated with a total base-case budget impact decrease in costs. Annual budget impact decrease in costs was CHF −6,747,073 in year 1 up to CHF 12,713,068 in year 5 and CHF 53,170,447 over the 5-year time horizon. The cost-comparison model showed an incremental cost decrease of CHF 2,675 per patient and CHF 988 per patient in years 1 and 5, respectively. A total incremental decrease in costs of CHF 8,326 per patient was found over the 5-year time horizon. Sensitivity analyses showed the budget impact analysis results were most sensitive to (1) the number of eligible incident patients, (2) first-year denosumab dosing of the monthly treatment arm, and (3) drug costs of denosumab. Cost-comparison results were most sensitive to (1) first-year denosumab dosing of the monthly treatment arm, (2) drug costs of denosumab, and (3) zoledronate and denosumab dosing of the 3-monthly treatment arm.

It should be noted that the model inputs were based on a variety of underlying assumptions, especially regarding the size of the target population, GP and nurse administration time, dosing, treatment discontinuation, and SRE probabilities and costs.

The only identified economic study found that there were no differences in effectiveness between the 2 treatment groups (monthly vs 3-monthly zoledronate of 0.90 and 0.91 QALYs, respectively, in year 1 and 0.91 and 0.91 QALYs, respectively, in year 2), supporting the findings from the meta-analysis of this HTA report. Mean zoledronate 3-monthly costs in 2015 USD were 5,667 and 9,290 for monthly zoledronate treatment. However, cost findings cannot be transferred to the Swiss context due to the differences in treatment costs.[88]

Potentially relevant information from an ongoing study was detected during the literature search. Results from the ongoing SAKK 96/12 trial (n=1,181) might strengthen the presented findings. Further studies investigating the role of bone markers in the treatment of BM are needed to support a uniform way of

reporting. Uniformity in reporting this outcome would enable a synthesis of results from different studies to gain more insight in the impact of BTA administration on bone markers.

Furthermore, supporting analyses of health insurance data to determine exact patient numbers and healthcare resource utilization costs would help to strengthen the economic model, since the main limiting factors are the assumptions made for the model parameters.

In summary, the analysis indicates no effect on clinical outcomes if dosing is switched to 3-monthly administration whilst providing a cost saving benefit to the Swiss healthcare system.

13 Conclusions

The scope of this HTA report was to assess whether the 3-monthly administration of licensed BTAs in Switzerland (zoledronate, ibandronate, and denosumab) in cancer patients with BM is equal to monthly administration in terms of efficacy/effectiveness and safety.

For ibandronate, no clinical evidence was identified, so results of this report may not be transferable to the extension of administration of the drug. Overall, extension of the dosing schedule of denosumab and zoledronate to 3-monthly administration was found to be associated with a similar risk of SREs, AEs, and SAEs as monthly administration of these BTAs. The findings, thus, indicate that extending the dosage frequency of BTAs may be reasonable from a clinical perspective; however, the analysis was driven by zoledronate studies and discrepancies in SRE subtype and rebound effect between different types of BTAs may need to be evaluated further.

Given the similarity in efficacy/effectiveness and safety, extended-interval dosing of BTAs may lead to a substantial reduction in annual direct costs per patient and, ultimately, in the annual budget impact in Switzerland.

Within the framework of this report, no evidence for social, legal, ethical, or organisational implications of frequency extension of BTAs was identified.

Evidence to evaluate the use of BTAs with different administration frequencies in cancer patients with BM remains scarce, limiting the ability to draw definitive conclusions.

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15 Appendices

15.1 Search strategies for the different databases

Appendix 1. Search strategies for the different databases

Database:	**Medline and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Daily and Versions**	
Interface:	**Ovid**	
Time segment:	**1946 to January 15, 2021**	
Date of search:	**18.01.2021**	
#	**Searches**	**Results**
1	exp Bone Neoplasms/ and exp Neoplasm Metastasis/ and exp Neoplasms/	11,625
2	(bone* adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	13,077
3	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	2,707
4	1 or 2 or 3	25,077
5	exp Bone Neoplasms/ and exp Neoplasm Metastasis/	11,625
6	((bone* neoplasm* or (bone* adj3 (cancer* or carcinom* or tumo?r*))) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	7,937
7	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (cancer* or carcinom* or tumo?r*) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	1,141
8	(bone* adj3 (metasta* or micrometasta*)).mp.	24,484
9	5 or 6 or 7 or 8	35,587
10	exp Multiple Myeloma/ or exp Plasmacytoma/	48,719
11	(solid* adj3 (malign* or neoplasm* or tumo?r*)).mp.	66,531
12	((multiple* adj4 myelom*) or (Kahler* adj2 diseas*) or (morbus adj2 kahler*) or (myeloma adj4 multiplex) or myelomatos#s or plasm##ytom* or ((plasma cell or plasmacell) adj4 myelom*)).mp.	61,831
13	10 or 11 or 12	127,541

14	9 and 13	1,912
15	4 or 14	25,628
16	(bone target* adj4 (therap* or agent*)).mp.	481
17	(bone modif* adj4 (therap* or agent*)).mp.	138
18	(BTA or BMA).ti,ab.	4,260
19	exp Zoledronic Acid/	3,509
20	(Zoledronic acid or Zoledronat? or Zometa or Zolacin or Aclasta or Orazol or Reclast or Zomera or cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or zol 446 or zol446).mp. or ZA.ti,ab.	7,233
21	exp Ibandronic Acid/	723
22	(Ibandronic acid or Ibandronat? or Bondronat? or Boniva or Bonviva or Ibandronico or bondenza or destara or iasibon or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or RPR-102289A or RPR102289A or r 484 or r484).mp.	1,221
23	(((receptor activator adj3 nuclear factor kappa B ligand) or RANKL or RANK-L or RANK ligand) adj4 (antibod* or inhibit*)).mp.	2,341
24	exp Denosumab/	1,727
25	(Denosumab or Xgeva or Prolia or Amgiva or amg 162 or amg162).mp.	3,360
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	16,976
27	exp Standard of Care/	4,097
28	(standard* adj4 (treatment* or care)).mp.	121,027
29	((health care or healthcare) adj4 (evaluation or quality)).mp.	162,253
30	exp Drug Therapy/	1,380,892
31	((Drug adj1 Therap*) or Chemotherap* or Pharmacotherap*).mp.	2,631,377
32	(dosing* or dosag* or dosis* or dose* or administration?).mp.	3,868,675
33	((drug adj2 infiltration*) or (drug adj2 injection*)).mp.	10,069
34	((drug* or administration* or dos*) adj4 (schedule* or interval*)).mp.	131,982
35	((De-escal* or deescal*) adj4 (therap* or treatment*)).mp.	1,048
36	(Dose-respons* adj4 evaluation*).mp.	349
37	((less adj4 intens*) or (frequen* adj4 treat*)).mp.	44,474
38	(3-4 week* or 3-4week* or 4 week* or 4week* or three week* or four week* or monthly or 1month*).mp.	257,360
39	(12 week* or 12week* or twelve week* or 3 month* or 3month* or three month*).mp.	354,302
40	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	6,236,187
41	15 and 26 and 40	1,384

42	41 and (exp Humans/ or human?.mp.)	1,223
43	41 not (exp Animals/ or (animal? or non-human? or nonhuman?).mp.)	145
44	42 or 43	1,346
45	limit 44 to (english or german or french)	1,245
46	limit 45 to yr=2000-2021	**1,228**
47	remove duplicates from 46	**1,222**

Database:	**Embase**	
Interface:	**Ovid**	
Time segment:	**1974 to January 15, 2021**	
Date of search:	**18.01.2021**	
#	**Searches**	**Results**
1	exp bone metastasis/ and exp malignant neoplasm/	46,150
2	(bone* adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	35,509
3	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	3,469
4	1 or 2 or 3	54,578
5	exp bone metastasis/	46,150
6	((bone* neoplasm* or (bone* adj3 (cancer* or carcinom* or tumo?r*))) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	12,480
7	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (cancer* or carcinom* or tumo?r*) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	1,696
8	(bone* adj3 (metasta* or micrometasta*)).mp.	60,653
9	5 or 6 or 7 or 8	63,182
10	exp solid tumour/	1,700,547
11	exp multiple myeloma/ or exp plasmacytoma/	86,107
12	(solid* adj3 (malign* or neoplasm* or tumo?r*)).mp.	126,890
13	((multiple* adj4 myelom*) or (Kahler* adj2 diseas*) or (morbus adj2 kahler*) or (myeloma adj4 multiplex) or myelomatos#s or plasm##ytom* or ((plasma cell or plasmacell) adj4	95,435

	myelom*)).mp.	
14	10 or 11 or 12 or 13	1,848,669
15	9 and 14	28,160
16	4 or 15	58,817
17	(bone target* adj4 (therap* or agent*)).mp.	783
18	(bone modif* adj4 (therap* or agent*)).mp.	229
19	(BTA or BMA).ti,ab.	4,847
20	exp zoledronic acid/	16,902
21	(Zoledronic acid or Zoledronat? or Zometa or Zolacin or Aclasta or Orazol or Reclast or Zomera or cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or zol 446 or zol446).mp. or ZA.ti,ab.	18,416
22	exp ibandronic acid/	5,407
23	(Ibandronic acid or Ibandronat? or Bondronat? or Boniva or Bonviva or Ibandronico or bondenza or destara or iasibon or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or RPR-102289A or RPR102289A or r 484 or r484).mp.	5,589
24	(((receptor activator adj3 nuclear factor kappa B ligand) or RANKL or RANK-L or RANK ligand) adj4 (antibod* or inhibit*)).mp.	3,709
25	exp denosumab/	9,475
26	(Denosumab or Xgeva or Prolia or Amgiva or amg 162 or amg162).mp.	9,940
27	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	34,650
28	exp health care quality/	3,352,106
29	(standard* adj4 (treatment* or care)).mp.	203,798
30	((health care or healthcare) adj4 (evaluation or quality)).mp.	269,305
31	exp drug therapy/	2,926,590
32	exp drug dose/	672,741
33	exp drug administration/	1,208,319
34	((Drug adj1 Therap*) or Chemotherap* or Pharmacotherap*).mp.	5,037,434
35	(dosing* or dosag* or dosis* or dose* or administration?).mp.	5,152,253
36	((drug adj2 infiltration*) or (drug adj2 injection*)).mp.	15,161
37	((drug* or administration* or dos*) adj4 (schedule* or interval*)).mp.	59,698
38	((De-escal* or deescal*) adj4 (therap* or treatment*)).mp.	2,087
39	(Dose-respons* adj4 evaluation*).mp.	474
40	((less adj4 intens*) or (frequen* adj4 treat*)).mp.	65,942
41	(3-4 week* or 3-4week* or 4 week* or 4week* or three week* or four week* or monthly or	397,778

	1month*).mp.	
42	(12 week* or 12week* or twelve week* or 3 month* or 3month* or three month*).mp.	578,254
43	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42	10,840,324
44	16 and 27 and 43	5,961
45	44 not Medline.cr.	5,732
46	45 and (exp human/ or human?.mp.)	5,450
47	45 not (exp animal/ or (animal? or non-human? or nonhuman?).mp.)	183
48	46 or 47	5,607
49	limit 48 to (english or german or french)	5,455
50	limit 49 to yr=2000-2021	5,404
51	50 and Conference Abstract.pt.	1,039
52	limit 51 to yr=1974-2014	582
53	50 not 52	**4822**
54	remove duplicates from 53	**3811**

Database:	**Cochrane Database of Systematic Reviews (CDSR)** **Database of Abstracts of Reviews of Effects (DARE)** **Health Technology Assessment (HTA)** **NHS Economic Evaluation Database (NHSEED)**	
Interface:	**Ovid**	
Time segment:	**CDSR - 2005 to December 31, 2020** **DARE - 1st Quarter 2016**	**HTA – 4th Quarter 2016** **NHSEED – 1st Quarter 2016**
Date of search:	**18.01.2021**	

#	Searches	Results
1	exp Bone Neoplasms/ and exp Neoplasm Metastasis/ and exp Neoplasms/	8
2	(bone* adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	101
3	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	25
4	1 or 2 or 3	120
5	exp Bone Neoplasms/ and exp Neoplasm Metastasis/	8
6	((bone* neoplasm* or (bone* adj3 (cancer* or carcinom* or tumo?r*))) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	89
7	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (cancer* or carcinom* or tumo?r*) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	18
8	(bone* adj3 (metasta* or micrometasta*)).mp.	176
9	5 or 6 or 7 or 8	196

10	exp Multiple Myeloma/ or exp Plasmacytoma/	111
11	(solid* adj3 (malign* or neoplasm* or tumo?r*)).mp.	343
12	((multiple* adj4 myelom*) or (Kahler* adj2 diseas*) or (morbus adj2 kahler*) or (myeloma adj4 multiplex) or myelomatos#s or plasm##ytom* or ((plasma cell or plasmacell) adj4 myelom*)).mp.	277
13	10 or 11 or 12	580
14	9 and 13	38
15	4 or 14	132
16	(bone target* adj4 (therap* or agent*)).mp.	5
17	(bone modif* adj4 (therap* or agent*)).mp.	5
18	(BTA or BMA).ti,ab.	10
19	exp Zoledronic Acid/	0
20	(Zoledronic acid or Zoledronat? or Zometa or Zolacin or Aclasta or Orazol or Reclast or Zomera or cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or zol 446 or zol446).mp. or ZA.ti,ab.	103
21	exp Ibandronic Acid/	0
22	(Ibandronic acid or Ibandronat? or Bondronat? or Boniva or Bonviva or Ibandronico or bondenza or destara or iasibon or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or RPR-102289A or RPR102289A or r 484 or r484).mp.	54
23	(((receptor activator adj3 nuclear factor kappa B ligand) or RANKL or RANK-L or RANK ligand) adj4 (antibod* or inhibit*)).mp.	11
24	exp Denosumab/	0
25	(Denosumab or Xgeva or Prolia or Amgiva or amg 162 or amg162).mp.	77
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	179
27	15 and 26	**45**

Database:	**Cochrane Central Register of Controlled Trials (CCTR)**	
Interface:	**Ovid**	
Time segment:	**December 2020**	
Date of search:	**18.01.2021**	
#	**Searches**	**Results**
1	exp Bone Neoplasms/ and exp Neoplasm Metastasis/ and exp Neoplasms/	198
2	(bone* adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	2,267
3	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*) adj6 (cancer* or carcinom* or neoplas* or tumo?r* or malign* or sarcom*)).mp.	219
4	1 or 2 or 3	2,487
5	exp Bone Neoplasms/ and exp Neoplasm Metastasis/	198
6	((bone* neoplasm* or (bone* adj3 (cancer* or carcinom* or tumo?r*))) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	2,021

7	((ilium or osseous or osteoblastic or osteoplastic or skeletal or skeleton or skull) adj3 (cancer* or carcinom* or tumo?r*) adj6 (metasta* or micrometasta* or micro-metasta* or recurren* or recrudesce* or secondary or spread*)).mp.	146
8	(bone* adj3 (metasta* or micrometasta*)).mp.	3,182
9	5 or 6 or 7 or 8	3,747
10	exp Multiple Myeloma/ or exp Plasmacytoma/	1,627
11	(solid* adj3 (malign* or neoplasm* or tumo?r*)).mp.	8,024
12	((multiple* adj4 myelom*) or (Kahler* adj2 diseas*) or (morbus adj2 kahler*) or (myeloma adj4 multiplex) or myelomatos#s or plasm##ytom* or ((plasma cell or plasmacell) adj4 myelom*)).mp.	5,648
13	10 or 11 or 12	13,457
14	9 and 13	397
15	4 or 14	2,606
16	(bone target* adj4 (therap* or agent*)).mp.	72
17	(bone modif* adj4 (therap* or agent*)).mp.	11
18	(BTA or BMA).ti,ab.	281
19	exp Zoledronic Acid/	0
20	(Zoledronic acid or Zoledronat? or Zometa or Zolacin or Aclasta or Orazol or Reclast or Zomera or cgp 42446 or cgp 42446a or cgp42446 or cgp42446a or zol 446 or zol446).mp. or ZA.ti,ab.	1,826
21	exp Ibandronic Acid/	0
22	(Ibandronic acid or Ibandronat? or Bondronat? or Boniva or Bonviva or Ibandronico or bondenza or destara or iasibon or "BM-21.0955" or "BM21.0955" or BM-210955 or BM210955 or RPR-102289A or RPR102289A or r 484 or r484).mp.	508
23	(((receptor activator adj3 nuclear factor kappa B ligand) or RANKL or RANK-L or RANK ligand) adj4 (antibod* or inhibit*)).mp.	267
24	exp Denosumab/	0
25	(Denosumab or Xgeva or Prolia or Amgiva or amg 162 or amg162).mp.	1,082
26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	3,375
27	exp Standard of Care/	281
28	(standard* adj4 (treatment* or care)).mp.	59,817
29	((health care or healthcare) adj4 (evaluation or quality)).mp.	10,363
30	exp Drug Therapy/	141,848
31	((Drug adj1 Therap*) or Chemotherap* or Pharmacotherap*).mp.	323,406
32	(dosing* or dosag* or dosis* or dose* or administration?).mp.	496,427
33	((drug adj2 infiltration*) or (drug adj2 injection*)).mp.	2,883
34	((drug* or administration* or dos*) adj4 (schedule* or interval*)).mp.	40,674
35	((De-escal* or deescal*) adj4 (therap* or treatment*)).mp.	270
36	(Dose-respons* adj4 evaluation*).mp.	314
37	((less adj4 intens*) or (frequen* adj4 treat*)).mp.	15,657
38	(3-4 week* or 3-4week* or 4 week* or 4week* or three week* or four week* or monthly or 1month*).mp.	99,889
39	(12 week* or 12week* or twelve week* or 3 month* or 3month* or three month*).mp.	160,692
40	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	840,821
41	15 and 26 and 40	518
42	41 and (exp Humans/ or human?.mp.)	408
43	41 not (exp Animals/ or (animal? or non-human? or nonhuman?).mp.)	379
44	42 or 43	518
45	limit 44 to yr=2000-2021	**514**
46	remove duplicates from 45	**283**

15.2 Inclusion and exclusion criteria

Appendix 2. Inclusion and exclusion criteria

Search	Inclusion criteria		Exclusion criteria
Population	• Cancer patients with bone metastases • Solid tumours (e.g., breast cancer, prostate cancer, lung cancer) • MM • Patients aged ≥18 years		• Cancer patients without BM • Cancer patients with BM not related to solid cancer/MM • Patients with diseases other than solid tumours and MM • Patients aged <18 years
Interventions	• Standard treatment with BTAs licensed in Switzerland • Bisphosphonates: o Zoledronate (IV every 3–4 weeks) o Ibandronate (IV every 3–4 weeks) • Denosumab (RANKL inhibitor) (SC every 4 weeks) • Standard dosing with BTA		All other interventions
Comparators	• De-escalated treatment with BTA (every 12 or more weeks) • De-escalated dosing with BTA • Reduced frequency BTA • Longer-interval dosing • Placebo	Bisphosphonates • Zoledronate (IV every 12 or more weeks) • Ibandronate (IV every 12 or more weeks) • RANKL • Denosumab (SC every 12 or more weeks)	• Standard treatment with BTAs • BTA dosing intervals <12 weeks • Treatment with another comparator than BTAs • Failed treatments (e.g., study discontinuation) due to consent withdrawal and disease progression

Search	Inclusion criteria		Exclusion criteria
Outcomes (clinical)	Efficacy: • SRE (critical) • New bone metastases • Skeletal morbidity rate • Recurrence of bone metastases • Bone pain • Usage of pain medication • General (health) condition/ performance status • Change of bone-related marker/marker of bone turnover (NTx, CTx), bone-specific alkaline phosphatase • Bone mineral density • Quality of life measures	Safety • Incidence of treatment-related AEs • Any AE • Severe AEs • Serious AEs • AEs leading to treatment discontinuation • AEs leading to study withdrawal/drop-out • Fatal AEs/all-cause mortality AEs include: • ONJ • Hypercalcaemia of malignancy • Infusion-related side effects • Renal toxicity (e.g., renal failure, renal impairment, decreased estimated glomerular filtration rate, decreased renal clearance) • Cardiovascular events	All other outcomes
Outcomes (economic)	• Budget impact • Costs (direct, medical, non-medical) • ICER, QALY, LY, and budget impact • Utilities • Costs per clinical event, LYG, QALY • Cost savings • Healthcare resource utilization		All other outcomes

Search	Inclusion criteria		Exclusion criteria
Study design/type	Clinical • RCTs and non-randomized controlled study • Observational studies (e.g., claims database studies, prospective cohorts, qualitative surveys, and cross-sectional studies) • Systematic reviews/ meta-analyses (for identification of primary studies) Economic • Randomized controlled and other trials that report cost or healthcare resource use data	Health economic All economic evaluations, such as: • Budget impact • Cost benefit • Cost utility • Cost effectiveness • Cost comparison Any relevant SLRs and meta-analyses will also be included for hand-searching of the reference lists	• Single-arm studies • Narrative review • Case reports, case series (N≤5) • *In vitro* studies • Animal studies
Publication language	English, French, German		All other
Publication type	Full publication		Non-pertinent publication types (e.g., editorials, expert opinions, letters to editor, conference/meeting abstracts, theses, and dissertations)
Setting	Clinical: Global	All other parts: Switzerland and focus on Western countries (Europe/United Kingdom, United States, Canada, Australia)	All other

Key: AE – adverse event; BM – bone metastases; BTA – bone-targeting agent; CTx – c-terminal telopeptide; ICER – incremental cost-effectiveness ratio; IV – intravenously; LY – life-year; LYG – life-year gained; MM – multiple myeloma; NTx – n-terminal telopeptide; ONJ – osteonecrosis of the jaw; QALY – quality-adjusted life-year; RANKL – receptor activator of nuclear factor kappa-B ligand; RCT – randomized controlled trial; SC – subcutaneously; SLR – systematic literature review; SRE – skeletal-related event.

15.3 List of excluded references

Appendix 3. List of excluded references

No full-text available

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Publication Type

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Outcome

Hortobagyi GN, Zheng M, Mohanlal R. Indirect evaluation of bone saturation with zoledronic acid after long-term dosing. *Oncologist*. 2019;24(2):178. http://theoncologist.alphamedpress.org http://dx.doi.org/10.1634/theoncologist.2018-0218

Tella SH, Kommalapati A, Singhi RK, Wu SG. Cost-effectiveness in managing skeletal related events in breast cancer: A strategy of less-intense dosing schedule of bone modifying agents. *Transl. Cancer Res*. 2018;7(Supplement1):S81. http://tcr.amegroups.com/article/download/18411/pdf http://dx.doi.org/10.21037/tcr.2018.01.07

Doshi S, Sutjandra L, Zheng J, Sohn W, et al. Denosumab dose selection for patients with bone metastases from solid tumours. *Clin Cancer Res*. 2012;18(9):2648. https://dx.doi.org/10.1158/1078-0432.CCR-11-2944.

Mark M, Thurlimann B, Ribi K, Schar C, et al. Patterns of care for patients with metastatic bone disease in solid tumours: a cross-sectional study from Switzerland (SAKK 95/16). *J Bone Oncol*. 2020;21:100273. https://dx.doi.org/10.1016/j.jbo.2019.100273

Duplicate

Continued efficacy and safety of zoledronic acid (q 4 wks vs. q 12 wks) in the 2nd year of treatment in patients with bone metastases from breast cancer. A prospective, randomized, double-blind, stratified, multi-center, 2-arm trial of the continued efficacy and safety of zoledronic acid (every 4 weeks vs. every 12 weeks) in the 2nd year of treatment in patients with documented bone metastases from breast cancer. 2006. https://clinicaltrials.gov/show/NCT00320710.

Zoledronic acid in treating patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma with bone involvement. A randomized, phase III study of standard dosing versus longer dosing interval of zoledronic acid in metastatic cancer. 2009. https://clinicaltrials.gov/show/NCT00869206

Safety and efficacy of zoledronic acid in patients with breast cancer with metastatic bone lesions. A prospective, randomized, multi-center comparative 2-arm trial of efficacy and safety of zoledronic acid (every 3-months vs. every 4 weeks) beyond approximately 1 year of treatment with zoledronic acid in patients with bone lesions from breast cancer. 2006 https://clinicaltrials.gov/show/NCT00375427

Denosumab (AMG 162) in bisphosphonate naive metastatic breast cancer. A randomized active-controlled study of amg 162 in breast cancer subjects with bone metastasis who have not previously been treated with bisphosphonate therapy. 2004. https://clinicaltrials.gov/show/NCT00091832

A randomized active controlled study of AMG 162 in breast cancer subjects with bone metastases who have not previously been treated with bisphosphonate therapy. 2004 http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2004-000509-24-AT

A prospective, randomized, multi-center comparative 2-arm trial on efficacy and safety of zoledronic acid every 3-months vs. every 4 weeks beyond approximately 1 year of treatment with zoledronic acid in patients with bone lesions from breast cancer - ND. 2006 http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2005-004942-15-IT

Fizazi K, Bosserman L, Gao G, Skacel T, Markus R. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: results of a randomized phase II trial. *J Urol.* 2009;182(2):509. https://dx.doi.org/10.1016/j.juro.2009.04.023.

Clemons M, Michael O, Stober C, Ernst S, et al. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. *Eur J Cancer.* 2021;(142):132.

Country

Hutton B, Morretto P, Emmenegger U, et al. Bone-targeted agent use for bone metastases from breast cancer and prostate cancer: a patient survey. *J Bone Oncol*. 2013;2(3):105. http://dx.doi.org/10.21037/tcr.2018.01.07.

Studies that were in the first screening step included for more than one HTA domain and excluded for the same reason multiple times were only listed once.

**Ongoing trials.*

15.4 Overview of the SLRs and MAs that included the identified RCTs/Non-RCTs

Appendix 4. Overview of the SLRs and MAs that included the identified RCTs/non-RCTs

SLR+MA / RCT+Non-RCT	Yang et al. 2020[74] P: mBC I/C: BP	Cao et al. 2017[70] P: cancer-related BM I/C: zoledronate	Awan et al. 2019[40] P: mBC I/C: BTA	Santini et al. 2019[73] P: BM in solid cancer I/C: zoledronate	O'Carrigan et al. 2017[72] P: mBC I/C: BTA	Ibrahim et al. 2015[71] P: mBC I/C: BTA	Luo et al. 2019[41] P: cancer-related BM I/C: BP	Liu et al. 2018[111] P: cancer-related BM I/C: BTA
Hortobagyi et al. 2017[62] P: mBC I/C: zoledronate Study design: RCT	X	X	X	X	X	X	X	X
Himelstein et al. 2017[77] P: cancer-related BM I/C: zoledronate Study design: RCT	X	X	X	X	X	-	X	X
Amadori et al. 2013[1] P: mBC I/C: zoledronate Study design: RCT	X	X	X	X	X	X	X	X
Novartis 2012[76] P: mBC + myeloma with BM I/C: zoledronate Study design: RCT	-	-	-	-	-	-	X	-
Lipton et al. 2007+2008[2 81] P: mBC I/C: denosumab Study design: RCT	-	-	X	-	-	X	-	X

Fizazi et al. 2009+2013[79 80] P: cancer-related BM I/C: denosumab Study design: RCT	-	-	-	-	X	X	-	X
Clemons et al. 2020[83] P: mBC, mCRPC I/C: zoledronate and denosumab Study design: RCT	-	-	-	-	-	-	-	-
Tam et al. 2020[78] P: mNSCLC and mSCLC I/C: zoledronate Study design: non-RCT	-	-	-	-	-	-	-	-
Abousaud et al. 2020[82] P: mBC, mPC, mLC I/C: denosumab Study design: non-RCT	-	-	-	-	-	-	-	-
Key: BM – bone metastases; BP – bisphosphonate; BTA – bone-targeting agent; I/C – intervention/comparator; MA – meta-analysis; mBC – metastatic breast cancer; mCRPC – metastatic castration-resistant prostate cancer; mLC – metastatic lung cancer; mNSCLC – metastatic non-small cell lung cancer; mSCLC – metastatic small cell lung cancer; mPC – metastatic prostate cancer; P – population; RCT – randomized controlled trial; SLR – systematic literature review.								

15.5 Ongoing RCT fitting the inclusion criteria

Appendix 5. Ongoing RCT fitting the inclusion criteria.

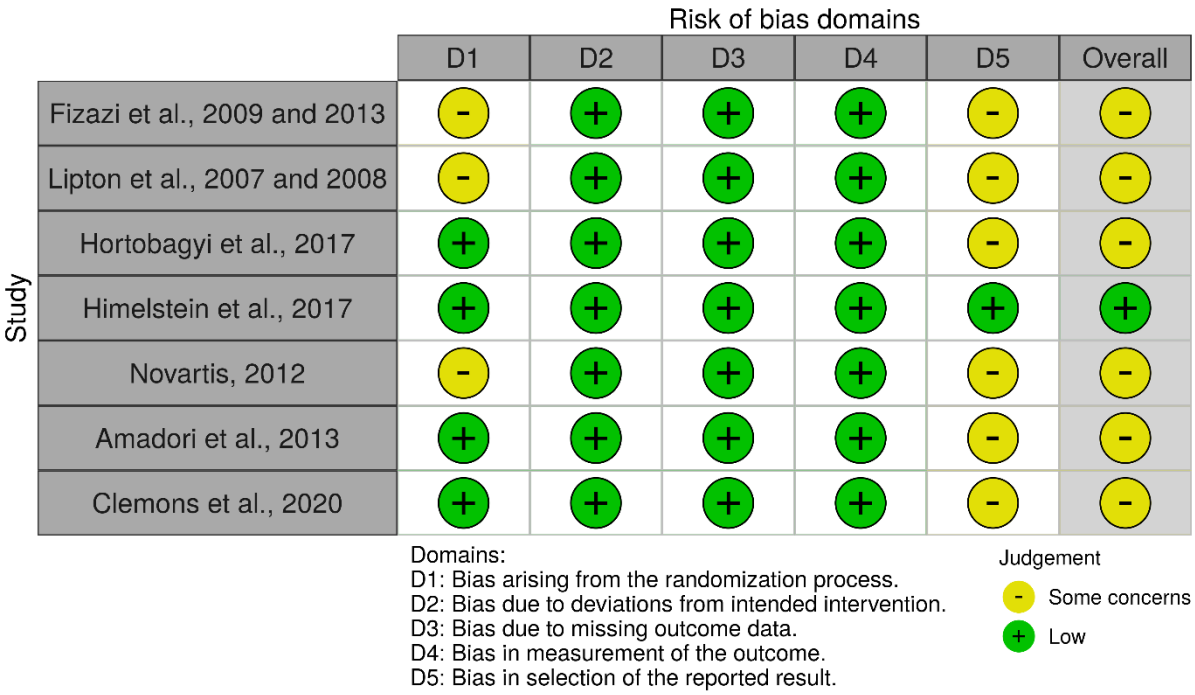
Trial name/registry ID	Study design	Population; n	Intervention	Comparator	Outcomes	Estimated completion date; status
SAKK 96/12[75] *NCT02051218*	• Phase 3, randomized, open-label, multicentre, international, noninferiority • 50 centres in Switzerland, Germany, and Austria	• mBC • mPC • Not previously treated with BTA n=1,380	Denosumab every 4 weeks	Denosumab every 2 weeks	• SSEs • SMRs • Overall survival • Quality of life measures • Bone markers • AEs/toxicity • Economic evaluations	December 2022; recruiting
Key: AE – adverse event; BTA – bone-targeting agent; mBC – metastatic breast cancer; mPC – metastatic prostate cancer; SMR – skeletal morbidity rate; SSE – symptomatic skeletal event.						

15.6 Risk of bias assessment for the included studies

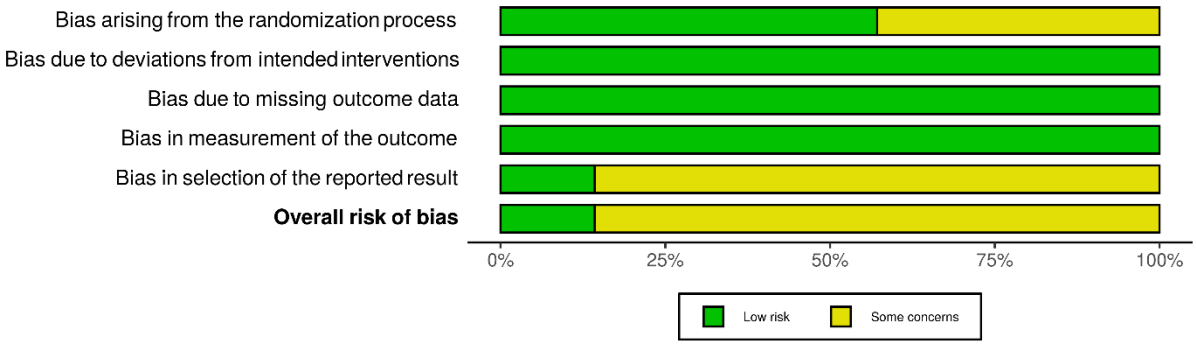
Appendix 6. Risk of bias assessment

1. RoB 2: RCTs

a. Traffic light plot

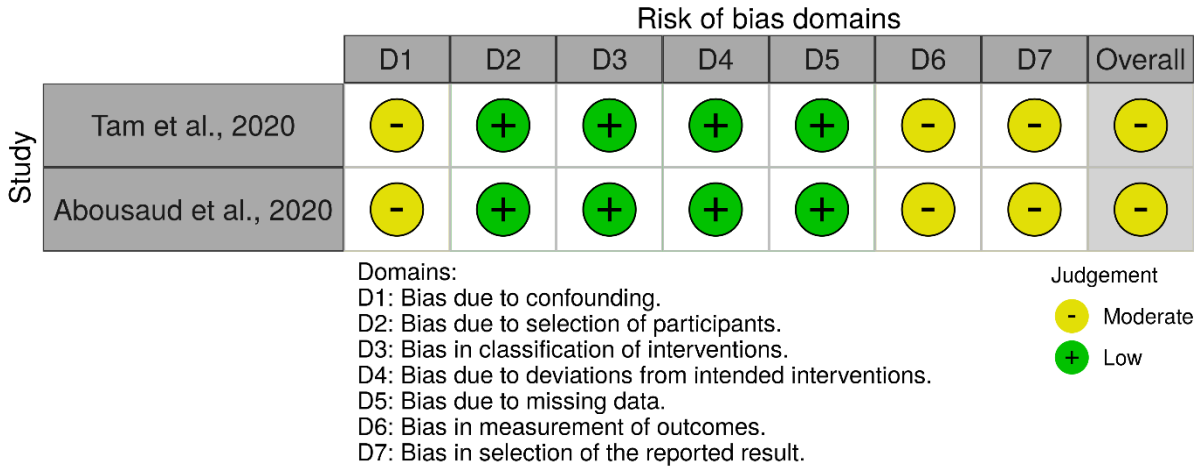


b. Summary plot

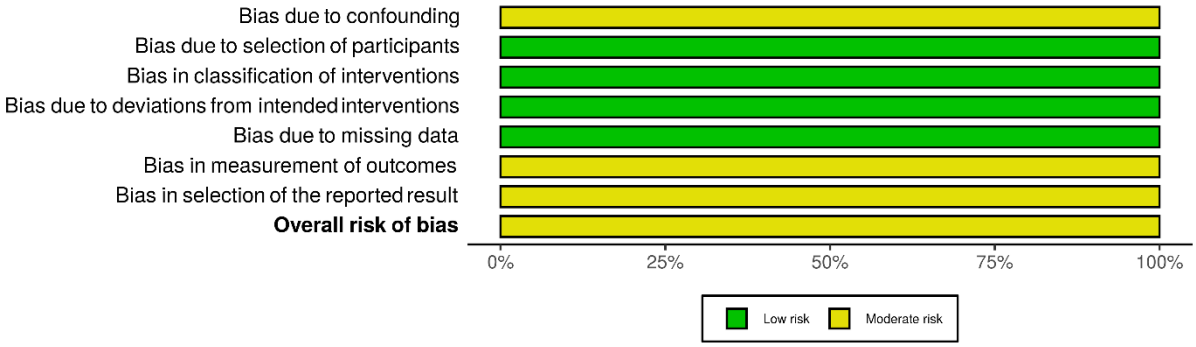


2. ROBINS-I: Non-RCTs

a. Traffic light plot



b. Summary plot



15.7 Conversion of Noninferiority Margins

Appendix 7. Conversion of Noninferiority Margins

The formular to convert the noninferiority margins reported as differences in absolute numbers is as follows[112]:

(X+Y)/X or **(X-Y)/X**

with X as the expected incidence of the outcome of interest and Y as the pre-specified noninferiority margin to be converted.

To calculate the corresponding noninferiority margin for the interpretation of the meta-analysis of this report, the assumed risk of the monthly administration was used for the expected incidence of the outcome of interest, calculated by dividing total events by total number of patients in the monthly treatment arm (see Table 13). The Cochrane guidance[113] proposes different approaches to calculate the assumed risk and described approach provided the narrowest results and was therefore chosen.

Study	Reported Margin	Converted Margin for RR Interpretation
Hortobagyi et al. 2017[62]	10%	(24+10)/24=1.42
Himelstein et al. 2017[77]	7%	(24+7)/24=1.29

15.8 CHEC-list to assess the included economic study

Appendix 8. CHEC-list for Shapiro et al.

	CHEC-list	Yes	No
1.	Is the study population clearly described?	X	
2.	Are competing alternatives clearly described?	X	
3.	Is a well-defined research question posed in answerable form?	X	
4.	Is the economic study design appropriate to the stated objective?	X	
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?		X
6.	Is the actual perspective chosen appropriate?	X	
7.	Are all important and relevant costs for each alternative identified?		X
8.	Are all costs measured appropriately in physical units?	X	
9.	Are costs valued appropriately?	X	
10.	Are all important and relevant outcomes for each alternative identified?	X	
11.	Are all outcomes measured appropriately?		X
12.	Are outcomes valued appropriately?		X
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	X	
14.	Are all future costs and outcomes discounted appropriately?	X	
15.	Are all important variables whose values are uncertain appropriately subjected to sensitivity analysis?		X
16.	Do the conclusions follow from the data reported?	X	
17.	Does the study discuss the generalizability of the results to other settings	X	

	and patient/client groups?		
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?		X
19.	Are ethical and distributional issues discussed appropriately?	X	

15.9 Trial Information to calculate annual SRE probabilities

Appendix 9. Trial Information according to the prescribing information of Xgeva®

	Study 20050136 mBC		**Study 20050244 Metastatic solid tumours or MM**		**Study 20050103 Metastatic castrate-resistant PC**	
	Denosumab N=1,026	Zoledronate N=1,020	Denosumab N=886	Zoledronate N=890	Denosumab N=950	Zoledronate N=951
Study duration	34 months		33 months		40.5 months	
N with at least 1 SRE	315	372	278	323	341	386
First and subsequent SRE (mean)	0.46	0.60	0.44	0.49	0.52	0.61
Components of first SRE						
N radiation to bone	82	119	119	144	177	203
N pathological fracture	212	238	122	139	137	143
N surgery to bone	12	8	13	19	1	4
N spinal cord compression	9	7	24	21	26	36
Key: mBC – metastatic breast cancer; MM – multiple myeloma; PC – prostate cancer; SRE – skeletal-related event.						