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# Bisphosphonates, teriparatide and denosumab for the treatment of postmenopausal osteoporosis[1]

## Extract

[1] Translation of Chapters 1 to 6 of the final report A19-10 *Bisphosphonate, Teriparatid und Denosumab zur Behandlung der postmenopausalen Osteoporose* (Version 1.0; Status: 2 November 2022 [German original], 28 June 2023 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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**Patient involvement**

Patients were consulted as part of the report preparation process.

Gisela Klatt took part in the discussion.

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Diphosphonates, Alendronate, Ibandronic Acid, Risedronic Acid, Zoledronic Acid, Teriparatide, Denosumab, Osteoporosis – Postmenopausal Benefit Assessment, Systematic Review

## Key statement

### *Research question*

The objective of this investigation is to assess the benefit of bisphosphonates, teriparatide, and denosumab in comparison with each other in the treatment of women with postmenopausal osteoporosis with regard to patient-relevant outcomes.

The research question includes an assessment of bisphosphonates in comparison with each other.

### *Conclusion*

Given the available evidence, the following individual comparisons were taken into account in the benefit assessment: denosumab versus bisphosphonates, teriparatide versus risedronate as well as bisphosphonates in comparison with each other.

For risedronate, the data transmission by the manufacturer was incomplete. Publication bias likely arose with respect to the risedronate intervention. Consequently, no proof, indication, or hint of benefit or harm is derived for the intervention of risedronate (except for a hint of lesser benefit from the comparison of teriparatide versus risedronate). In the comparison of teriparatide versus risedronate, the incompleteness of the manufacturer documents was irrelevant because all studies were available on this comparison.

The available evidence for patient-relevant outcomes is deemed limited overall. The available evidence was insufficient, particularly for the outcomes of pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, and symptomatic atypical femoral fractures.

*Comparison of denosumab versus bisphosphonates*

For the comparison of denosumab versus bisphosphonates, the available data allow drawing robust conclusions only in comparison with the drug zoledronate.

The evidence shows the following:

- No hint of greater benefit or harm resulted from the available data for the outcomes of all-cause mortality, fractures in the hip area, distal radius fractures, symptomatic vertebral fractures, nonvertebral symptomatic fractures, serious adverse events (SAEs), discontinuation due to adverse events (AEs) as well as AEs and SAEs of the gastrointestinal tract.

- For the outcomes of pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, and symptomatic atypical femoral fractures, no data usable for the comparison of denosumab versus bisphosphonates were available; therefore, no hint of greater benefit or harm resulted for any of them.

In the overall weighing of benefit and harm, there was no hint of greater or lesser benefit or harm for treatment with denosumab in comparison with zoledronate across outcomes.

*Comparison of teriparatide versus risedronate*

For the comparison of teriparatide versus risedronate, which can be conducted given the available data, the evidence shows the following:

- For the outcome of symptomatic vertebral fractures, there was a hint of greater benefit of teriparatide versus risedronate.

- For the outcome of AEs of the gastrointestinal tract, there was a hint of greater harm from teriparatide versus risedronate.

- No hint of greater benefit or harm was found on the basis of the available data for the outcomes of all-cause mortality, fractures in the hip area, distal radius fractures, nonvertebral symptomatic fractures, pain, SAEs, discontinuation due to AEs, osteonecrosis of the jaw, and symptomatic atypical femoral fractures as well as SAEs of the gastrointestinal tract.

- No data were available for the outcomes of functional limitations or health-related quality of life; this resulted in no hint of greater harm or benefit.

Overall, the favourable effect for teriparatide in comparison with risedronate in the outcome of symptomatic vertebral fractures is therefore contrasted by an unfavourable effect for teriparatide in comparison with risedronate in the outcome of AEs of the gastrointestinal tract. Given the fact that the outcome of symptomatic vertebral fractures showed a substantial effect in favour of teriparatide (upper limit of the 95% confidence interval: 0.58), while the disadvantage was marginal in the outcome of AEs of the gastrointestinal tract (95% confidence interval: [1.01; 1.57]) and not present in SAEs of the gastrointestinal tract, the overall weighing of benefit and harm across outcomes resulted in a hint of greater benefit of teriparatide versus risedronate.

*Bisphosphonates in comparison with each other*

For the comparison of bisphosphonates with each other, robust conclusions based on the available data can be drawn only for the drugs of alendronate and ibandronate.

The evidence shows the following:

- No hint of greater benefit or harm was found based on the available data for the outcomes of fractures in the hip area, distal radius fractures, nonvertebral symptomatic fractures, SAEs, discontinuation due to AEs, or AEs and SAEs of the gastrointestinal tract.

- No data were available for the outcomes of all-cause mortality, symptomatic vertebral fractures, pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, and symptomatic atypical femoral fractures; this resulted in no hint of greater benefit or harm for any of them.

In the overall weighing of benefit and harm, there was no hint of greater or lesser benefit or harm of alendronate versus ibandronate across outcomes.

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| BMD | bone mineral density |
| BMI | body mass index |
| DXA | dual-energy X-ray absorptiometry |
| FRAX | Fracture Risk Assessment Tool |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| PT | Preferred Term |
| RCT | randomized controlled trial |
| SERM | selective oestrogen receptor modulator |
| SOC | System Organ Class |
| WHO | World Health Organization |

# 1 Background

## Pathogenesis and progression of postmenopausal osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1-5]. Due to age-related bone loss, the prevalence of osteoporosis rises with increasing age [6]. Since menopause causes a drop in the oestrogen level, bone loss is further accelerated in postmenopausal women [7].

## Definition and diagnosis of postmenopausal osteoporosis

According to the widely used criteria specified by the World Health Organization (WHO), osteoporosis is diagnosed at a T-score of $\leq -2.5$ standard deviations from the mean score in 20 to 29-year-old women as measured via dual-energy X-ray absorptiometry (DXA) [2,5,8]. Central DXA scans are performed in the lumbar spine and/or the proximal femur [2]. Alongside the commonly used DXA, other central densitometry techniques such as quantitative computed tomography (QCT) are available, and these techniques are preferred to peripheral densitometry, measured in locations such as the forearm [2,4,5]. DXA scans are to be used as the standard method for diagnosing osteoporosis [5]. Densitometry at the proximal femur and the lumbar spine is preferred, although scans of the spine may be of limited interpretive value, e.g. due to age-related deterioration of vertebrae [1,5].

Postmenopausal osteoporosis is a form of primary osteoporosis, meaning that it is not caused by (a) any other diseases, (b) immobilization, or (c) side effects of drug therapies [1]. Osteoporosis is of clinical importance due to the occurrence of bone fractures and their consequences [1,5]. These fractures most often involve the spine or vertebrae, the forearm or wrist (distal radius), and the hip (proximal femur), but they can also occur in the arm (humerus), pelvis, ribs, or other bones [1,6,8,9].

Alongside bone density, bone characteristics such as microarchitecture and degree of mineralization affect bone stability [1,2]. At reduced bone stability, even low-trauma events, such as falls from standing or sitting height may result in fractures [2]. Osteoporosis is called manifest if a fracture occurs as a result of a low-trauma event [5,10]. However, many women with such fractures do not exhibit a bone mineral density (BMD) T-score $\leq$ -2.5 (threshold defined by the WHO [1]). BMD alone does not reliably predict the risk of bone fractures [1,8,9,11]. According to treatment guidelines, the operationalization of osteoporosis as per WHO criteria falls short. Instead, guidelines indicate that the need for treatment is determined by the estimated fracture risk, which is in turn based on both bone density and additional factors [5,10].

## Fracture risk and indication for therapy

Patients at substantially increased risk of fractures should receive drug treatment to reduce their fracture risk [5]. Whether a patient is indicated for therapy should be determined based on absolute fracture risk rather than resting solely on the BMD score [2,4,5]. Guidelines list various

risk prediction models such as the QFracture risk score, the Fracture Risk Assessment Tool (FRAX), the Garvan fracture risk calculator, and the model by the German Umbrella Association of Osteoporosis (DVO model) [12]. These models take into account various risk factors [12]. In addition to age, body mass index (BMI), (family) history of fractures, alcohol and tobacco use as well as secondary causes of osteoporosis (e.g. specific underlying illnesses such as rheumatoid arthritis and drug treatments such as glucocorticoid therapy), different models take into account further factors which may additionally affect fracture risk [12]. For instance, the DVO lists frequent intrinsic falls or immobility as further risk factors [5]. None of these models have been shown to be clearly superior to any other [5,8,9,13]. Guidelines as well as the European Medicines Agency (EMA) recommend using the 10-year absolute fracture risk [1,5,9,12]. Depending on the determined 10-year risk, osteoporosis therapy is already recommended at a BMD T-score < -2, or – under certain circumstances – even at ≥ -2 [5,10]. In terms of being indicated for treatment, a 10-year risk above 30% of radiographic fractures at vertebrae or femur fractures as calculated by the DVO model is deemed equivalent to a 14% risk of major fractures as per FRAX (clinical fractures of the vertebrae as well as fractures of the hip, humerus, or wrist [8]) [5].

**Goals of treatment**

The goal of diagnosing osteoporosis and the subsequent intervention is to prevent fractures. Fractures are associated with pain, potentially major and/or permanent functional limitations, and reduced health-related quality of life. Women who suffer hip fractures, vertebral fractures, or other major nonvertebral fractures are at a higher mortality risk [1,2,8]. In itself, bone density loss is not noticeable, and in the therapeutic indication of osteoporosis, increased bone density is not a suitable surrogate for reduced fracture incidence [1]. Consequently, fracture avoidance is the primary treatment goal [5,10].

**Osteoporosis treatment and guideline recommendations**

Postmenopausal osteoporosis can be pharmacologically treated both to reduce bone loss (antiresorptive agents such as bisphosphonates [also referred to as diphosphonates] and denosumab) and to promote bone regeneration (teriparatide as a fragment of parathormone). Other drug treatment options are available, e.g. bazedoxifen, raloxifen, and oestrogens [5]. During the therapy of postmenopausal osteoporosis, sufficient exercise and an adequate supply of calcium and vitamin D should be ensured [5,14].

At the time of commissioning by the Federal Joint Committee (G-BA), the bisphosphonates alendronate, ibandronate, risedronate, and zoledronate (including combinations with alfacalcidol, cholecalciferol, or calcium) were available in Germany for the treatment of postmenopausal osteoporosis. The commission ordered by the G-BA further comprises the drugs of teriparatide and denosumab.

At the time the final report is written, international and British guidelines recommend treatment with an oral bisphosphonate (alendronate, risedronate, or ibandronate) as first-line therapy [8,9]. Bisphosphonates in intravenous formulations (zoledronate or ibandronate) as

well as denosumab represent other potential options for (first-line) therapy [9,10]. These drugs are recommended particularly for patients with contraindications or intolerance to oral bisphosphonates [8–10]. The anabolic agent teriparatide is recommended for patients at high [8] or very high fracture risk [9,10] or for secondary prevention in patients with existing fractures. The guideline for German-speaking countries does not include a specific treatment algorithm. Rather, it recommends individualized weighing of risks against benefits, taking into account factors such as potential side effects and additional effects, the proven duration of effect after discontinuation of the preparations, and administration modalities [5]. Because the illness is often of long duration, treatment sequences are gaining in importance as treatment strategies [15,16].

Different network metaanalyses (NMAs) have compared diverse osteoporosis medications with regard to fractures in various patient populations [17–22]. To date, it is unclear how the above investigational substances interact in postmenopausal women with osteoporosis in terms of patient-relevant outcomes, even beyond fractures.

## 2 Research question

The objective of this investigation is to

- assess the benefit of bisphosphonates, teriparatide, and denosumab in comparison with each other

in the treatment of women with postmenopausal osteoporosis with regard to patient-relevant outcomes.

The research question includes an assessment of bisphosphonates in comparison with each other.

# 3 Methods

The target population of the benefit assessment comprises postmenopausal women who are indicated for treatment of postmenopausal osteoporosis. The population was defined not exclusively by bone density scores, but also by clinical factors (e.g. age, [family] history of fractures). Bisphosphonates, teriparatide, and denosumab for the treatment of postmenopausal osteoporosis were to be compared with each other; therefore, each of them represented both an investigational and a comparator intervention.

The following patient-relevant outcomes were taken into account in the investigation:

- All-cause mortality
- Fractures
  - fractures in the hip area
  - distal radius fractures
  - symptomatic vertebral fractures
  - nonvertebral symptomatic fractures
- Pain
- Functional limitations
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - osteonecroses of jaw (ONJs)
  - symptomatic atypical femoral fractures (AFFs)
  - AEs of the gastrointestinal tract

Only randomized controlled trials (RCTs) with a minimum duration of 2 years were included in the benefit assessment.

The systematic literature search for studies was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase and the Cochrane Database of Systematic Reviews.

In addition, the following information sources and search techniques were taken into account: study registries, manufacturer queries, publicly accessible documents from regulatory

authorities, G-BA and IQWiG websites as well as the screening of reference lists, documents made available from hearing procedures, and author queries.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, outcome-specific and study-level criteria for the risk of bias were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were described, organized by outcomes.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

For each outcome, a conclusion was drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

The network metaanalysis technique, which was to be used for the present benefit assessment, required checking the similarity of the studies to be entered into the network. To ensure sufficient similarity of the studies in the pool, the fracture risk of participants is to be estimated as a key factor for the similarity assumption. To assess with sufficient certainty the fracture risk and similarity of the studies with regard to participants' fracture risk, studies had to provide, at minimum, information on the 4 factors of age, T-score, BMI (or height and weight), and existing fractures. Using these data, participants' fracture risk was first qualitatively assessed based on the overall picture of these patient characteristics. To objectify this qualitative assessment of fracture risk, an estimate of the 10-year fracture risk for major osteoporotic fractures (fractures near the hip joint, clinical vertebral fractures, arm and forearm fractures) was additionally calculated using the FRAX [23–25]. These calculations were based on the information on the 4 above-mentioned factors, taking into account the region where the studies were conducted.

# 4 Results

## 4.1 Results of the information retrieval

The information retrieval resulted in 37 RCTs relevant for the research question.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search in bibliographical databases was conducted on 4 December 2019 and the last search in study registries on 8 January 2020.

Table 2: Study pool of the benefit assessment (multipage table)

| Study | Available documents | | | |
|---|---|---|---|---|
| | **Full publication (in scientific journals)** | **Registry entry / result report from trial registries** | **Clinical study report from manufacturer documents (not publicly available)** | **Other documents** |
| 20080756[a] | Yes [26] | Yes [27] / no | No | No |
| 5RO1 ARO5[a] | Yes [28,29] | Yes [30] / no | No | No |
| ARCH[a] | Yes [31.32] | Yes [33-35] / yes | No | Yes [36] |
| B3D-JE-GHDB[a] | Yes [37–39] | Yes [40] / yes | Yes [41] | No |
| B3D-MC-GHBQ[a] | Yes [42] | Yes [43] / no | No | No |
| Bai 2013 | Yes [44] | No | No | No |
| Carfora 1998[a] | Yes [45] | No | No | No |
| CL3-12911-019[a] | Yes [46,47] | Yes [48,49] / yes | No | No |
| CL3-12911-030[a] | No | Yes [50] / yes | No | No |
| DIRECT | Yes [51,52] | Yes [53,54] / yes | No | No |
| DIVA[a] | Yes [55-59] | Yes [60-62] / yes | Yes [63,64] | No |
| El-Hamamsy 2016[a] | Yes [65] | No | No | No |
| EUROFORS[a] | Yes [66-70] | Yes [71] / no | Yes [72] | No |
| Evio 2004[a] | Yes [73,74] | No | No | No |
| Frediani 1998[a] | Yes [75] | No | No | No |
| FREEDOM | Yes [76–121] | Yes [122–125] / yes | Yes [126] | No |
| Gonelli 1999[a] | Yes [127] | No | No | No |
| Guanabens 2013 | Yes [128] | No | No | No |
| HORIZON-PFT | Yes [113,129–151] | Yes [152] / no | Yes [153] | No |
| Kuzmanova 2011[a] | Yes [154] | No | No | No |
| Liang 2017[a] | Yes [155] | No | No | No |
| MK0217-035 | Yes [156–164] | No | Yes [165] | No |
| MK0217-037 | Yes [156–163] | No | Yes [166] | No |
| MK0217-041 | No | No | Yes [167] | No |
| MK0217-063 | No | No | Yes [168] | No |
| MK0217-072[a] | Yes [169,170] | No | Yes [171] | No |
| MK0217-118[a] | No | No | Yes [172] | No |
| MOBILE[a] | Yes [173–178] | Yes [179–181] / yes | Yes [182][b] | No |
| Muscoso 2004[a] | Yes [183] | No | No | No |
| Nakamura 2017[a] | Yes [184.185] | Yes [186] | No | No |
| Peretz 2003[a] | Yes [187] | No | No | No |
| Rizzoli 2002[a] | Yes [188] | No | No | No |
| Sosa 2002[a] | Yes [189] | No | No | No |
| Tan 2016[a] | Yes [190] | No | No | No |
| Tascioglu 2005[a] | Yes [191] | No | No | No |
| TRIO | Yes [192-194] | Yes [195,196] / yes | No | No |
| VERO | Yes [197-202] | Yes [203,204] / yes | Yes [205] | No |

Table 2: Study pool of the benefit assessment (multipage table)

| Study | Available documents | | | |
|---|---|---|---|---|
| | **Full publication (in scientific journals)** | **Registry entry / result report from trial registries** | **Clinical study report from manufacturer documents (not publicly available)** | **Other documents** |
| a. The study meets the inclusion criteria but had to be disregarded below for the benefit assessment. The reasons are presented in Section A3.2 of the full report.<br>b. The manufacturer sent a study report after 1 year of treatment; however, said study report is irrelevant for the benefit assessment (see Section A3.1.1.3 of the full report). | | | | |

No relevant studies without reported results were identified. However, relevant study documents on risedronate are missing for 17 studies due to incomplete data transmission by the manufacturer, with further test steps revealing that 2 of these studies fail to meet the inclusion criterion I8 (minimum duration). Twelve of the remaining 15 studies compared risedronate versus placebo and were therefore potentially relevant for a network. Hence, publication bias is likely for the intervention of risedronate. Consequently, no proof, indication, or hint of benefit or harm is derived for the intervention of risedronate [206] (except for a hint of lesser benefit from the comparison of teriparatide versus risedronate; see Section 4.3.5).

After the available studies and study documents were identified, the study pool was checked for the studies' suitability for a network metaanalysis. From the 37 studies in the study pool, a total of 18 studies were unusable for further test steps. Sixteen of the 18 studies contained neither a direct comparison of the interventions of interest nor comparator interventions which would lend themselves to use as suitable common comparators in indirect comparisons within the study pool because no other study used a similar comparator intervention. In 2 of the 18 studies, the intervention was a treatment sequence with multiple consecutive drugs (teriparatide followed by raloxifene). Due to the absence of a relevant comparator intervention, these 2 studies were disregarded.

This left 19 studies remaining in the study pool; for these studies, the similarity assumption was to be checked in the network metaanalysis. As a key factor for the similarity assumption, the fracture risk of study participants was to be assessed. The 4 factors of age, T-score, BMI (or height and weight), and existing fractures are essential for assessing fracture risk [1,5,23]. At minimum, studies therefore had to supply information on these 4 factors in order to allow assessing with sufficient certainty (a) fracture risk and (b) the studies' similarity with regard to participants' fracture risk. A total of 8 of the 19 studies, however, failed to provide information on all 4 factors defined the minimum required information. Reliably assessing the fracture risk was therefore impossible. Hence, these 8 studies were excluded from further analysis. It should be noted that these 8 studies provided very limited information on individual patient-relevant outcomes. Disregarding these studies from further analysis therefore did not exclude relevant information from the benefit assessment.

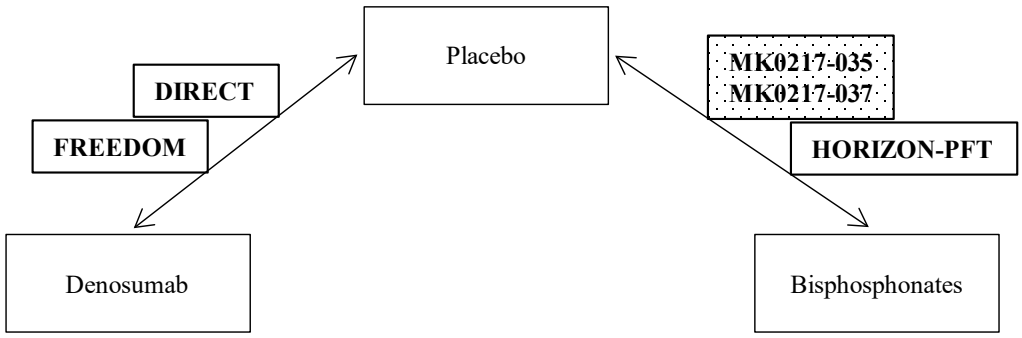
A total of 11 studies thus remained for the similarity check.

The joint analysis of the qualitative assessment of fracture risk based on the above-described 4 factors of age, T-score, BMI (or height and weight), and existing structures as well as a quantitative assessment of fracture risk by means of the FRAX (see details in Section A3.2 of the full report) resulted in the following rating for these 11 studies:

- In the HORIZON-PFT, DIRECT, FREEDOM, and VERO studies, participants' fracture risk was deemed high overall.
- In the MK0217-037, -041, -063, Bai 2013, and Guanabens 2013 studies, participants' fracture risk was rated as lower than in the studies listed above.
- The participants of the MK0217-035 and TRIO studies were estimated to be at moderate fracture risk.

Given the available data, it was impossible to create a complete network including all drugs. Figure 1 shows the observed indirect and direct comparisons.

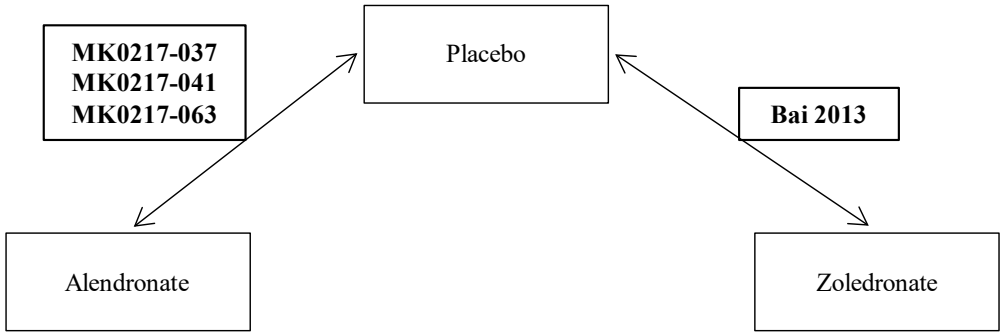
**Denosumab vs. bisphosphonates: indirect comparison**



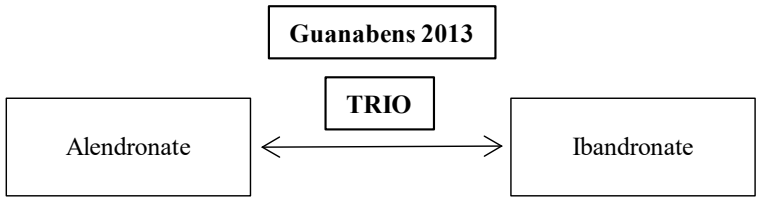

**Teriparatide vs. risedronate: direct comparison**


**Bisphosphonates: comparison with each other**

**Indirect comparison[a]**




**Direct comparison**




a. The indirect comparison of bisphosphonates with each other was not carried out. Details are described in the text below or in Section 4.4. Boxes with dotted background: The MK0217-035 and MK0217-037 studies were added in the context of a sensitivity analysis because fracture risk was not deemed high in these studies – unlike in the other 3 studies comparing denosumab versus bisphosphonates.

Study names are presented in capital letters or bold.

Figure 1: Indirect and direct comparisons examined in light of the currently available evidence

Overall, the following comparisons were taken into account based on the available evidence.

- **Comparison of denosumab versus bisphosphonates**

  An adjusted indirect comparison using the common comparator of placebo was conducted for the interventions of denosumab and bisphosphonates. This comparison first analysed the 3 studies exhibiting similar fracture risk, with their participants being at high fracture risk. The further factors taken into account in the check of similarity (see Section A3.2 of the full report) were likewise deemed sufficiently similar between these studies. On the denosumab-placebo edge, these were the DIRECT and FREEDOM studies. Hence, only the HORIZON-PFT study comparing zoledronate versus placebo was initially analysed on the placebo-bisphosphonate(s) edge. An adjusted indirect comparison between denosumab and zoledronate was therefore conducted as the main analysis.

  A supplementary sensitivity analysis jointly analysed the studies which enrolled participants at high and moderate fracture risk. The studies were sufficiently similar with regard to the other investigated factors. For the bisphosphonate(s)-placebo edge, the sensitivity analysis used the HORIZON-PFT study as well as the MK0217-035 study comparing alendronate versus placebo. In the latter, participants' fracture risk is deemed moderate. For this edge, its sister study MK0217-037 was additionally included; according to qualitative assessments, at least, this study's participants have a fracture risk comparable to those of the MK0217-035 study. Hence, the sensitivity analysis investigated an adjusted indirect comparison of denosumab versus zoledronate and alendronate. These analyses can be performed only for the outcomes for which data are available in the MK0217-035 and -037 studies. The results of the main analysis and the sensitivity analysis are described in Section 4.2.

- **Comparison of teriparatide versus risedronate**

  It was impossible to link the VERO study, whose participants' fracture risk was deemed high, to other studies via a shared node in a network or in the form of an indirect comparison. The results on the comparison of teriparatide versus risedronate are presented separately in the form of a direct comparison. In this case, the manufacturer documents being incomplete regarding risedronate is irrelevant because (a) there was no connection to a network and (b) all studies were available for the separate presentation of results on this comparison. For the direct comparison of teriparatide versus risedronate, the manufacturer documents were complete. The results are described in Section 4.3.

- **Comparison of bisphosphonates with each other**

  The studies in participants at low fracture risk were suitable for performing an adjusted indirect comparison of alendronate (MK0217-037, -041, -063 studies) versus zoledronate (Bai 2013 study) via the common comparator of placebo. This involved comparing 2 bisphosphonates with each other. However, the adjusted indirect comparison was foregone due to the studies' missing data on patient-relevant outcomes. This is explained in detail in Section 4.4.

In addition, the studies Guanabens 2013 (alendronate versus ibandronate) and TRIO (alendronate versus ibandronate versus risedronate), whose participants' fracture risk was deemed low or moderate, yielded a direct comparison of the bisphosphonates alendronate versus ibandronate in the form of a potential metaanalysis. This analysis disregarded the additional risedronate arm of the TRIO study. However, conducting a metaanalysis was impossible given the available evidence. Section 4.4 describes the available evidence and results.

Table 3 shows an overview of the 11 studies ultimately taken into account, with the respective comparisons performed.

Table 3: Studies ultimately taken into account and allocation to direct and indirect comparisons

| **Comparison foregone due to lack of available data** | |
|---|---|
| **Study (study start)** | **Comparison** |
| MK0217-037 (1991) | Adjusted indirect comparison of alendronate versus zoledronate (Section 4.4) |
| MK0217-041 (1991) | |
| MK0217-063 (1993) | |
| Bai 2013 (2008) | |
| **Comparisons conducted in light of the available evidence** | |
| **Study (study start)** | **Comparison** |
| DIRECT (2008) | Adjusted indirect comparison of denosumab versus zoledronate (Section 4.2) |
| FREEDOM (2004) | |
| HORIZON-PFT (2002) | |
| MK0217-035 (1991) | Sensitivity analysis on the adjusted indirect comparison of denosumab versus zoledronate and alendronate (Section 4.2) |
| MK0217-037 (1991) | |
| VERO (2012) | Direct comparison of teriparatide versus risedronate (Section 4.3) |
| TRIO (2007) | Direct comparison of alendronate versus ibandronate (Section 4.4) |
| Guanabens 2013 (2007) | |

## 4.2 Comparison of denosumab versus bisphosphonates

Given the available evidence, the study pool for the investigation of denosumab versus bisphosphonates consists of 3 sufficiently similar studies whose participants are at high fracture risk (DIRECT, FREEDOM, HORIZON-PFT). Two further studies with participants at moderate fracture risk (MK0217-035 and MK0217-037) were added in a sensitivity analysis (see Table 19 and Table 20 in Section A3.2 of the full report). In principle, the studies provided data for an adjusted indirect comparison.

### 4.2.1 Characteristics of the studies included in the assessment

**Study design**

The FREEDOM [89], HORIZON-PFT [130], MK0217-035 [161], and MK0217-037 [161] studies and the arms of the DIRECT [51] study which are relevant for the present comparison had a double-blind design. The studies were multicentric, with the DIRECT study being conducted only in Japan, the MK0217-035 study only in the United States, and the other 3 studies worldwide. The oldest studies started in 1991 (MK0217-035, MK0217-037) and 2002 (HORIZON-PFT), while the most recent study started in 2008 (DIRECT). The study phase relevant for the present benefit assessment had a duration of either 2 or 3 years in all studies.

At 7736 or 7808 patients, the HORIZON-PET and FREEDOM studies had the largest patient populations among the included studies.

The DIRECT and FREEDOM studies examined the intervention denosumab (60 mg every 6 months) versus placebo. The DIRECT study had an additional alendronate arm in which 35 mg/week of alendronate was administered. This dosage departs from the alendronate marketing authorization [207,208]. The DIRECT study's alendronate arm is therefore irrelevant for the present benefit assessment and is disregarded below. The HORIZON-PFT study investigated the zoledronate intervention (5 mg/year) versus placebo. The MK0217-035 and MK0217-037 studies compared alendronate in daily doses of 5 mg, 10 mg, and 20 mg versus placebo. The 5 mg and 20 mg doses depart from the alendronate marketing authorization [207,208]. The alendronate 5 mg and 20 mg study arms are therefore irrelevant for the benefit assessment and disregarded below.

As primary outcomes, the studies examined vertebral or hip fractures (DIRECT, FREEDOM, HORIZON-PFT) or BMD at the lumbar spine (MK0217-035, MK0217-037). Further surveyed patient-relevant outcomes included side effects and – in the FREEDOM and HORIZON-PFT studies – other patient-relevant fracture outcomes, health-related quality of life, pain, or functional limitations.

**Study populations**

Except in the DIRECT study, the study populations comprised only women, largely of Caucasian descent.

The studies' mean participant age ranged from 69 to 73 years, with a mean of 63 years in MK0217-035 and 64 years in MK0217-037. The fracture risk factor of BMI slightly differed between the studies, at means between 22 and 26 kg/m$^2$. Data on participants' mean body weight (59 kg to 64 kg) and height (153 cm to 160 cm) were available for all studies except DIRECT.

All studies reported data on BMD at the femoral neck (mean T-score between -2.2 and -2.7), and all but the HORIZON-PFT study provided participants' BMD at the lumbar spine (mean T-score < -2.5 to -2.8).

The study documents contain scant data on other fracture risk factors. For instance, only 1 study (FREEDOM) provides data on 10-year risk for fractures, and only 2 studies (MK0217-035, MK0217-037) deliver information regarding participants' family history of osteoporosis. Patients with existing vertebral fractures made up 17% to 28% of participants in the MK0217-035, MK0217-037, and FREEDOM studies, 63% in the HORIZON-PFT study, and 98% in the DIRECT study. The number of participants with existing nonvertebral fractures was reported only in the FREEDOM study (about 39%). None of the studies provided any data on the number of participants with existing hip fractures.

With the exception of the DIRECT study, all studies reported information on participants with relevant treatment at baseline. About 13% of patients included in the MK0217-035 and MK0217-037 studies, about 21% of those in the HORIZON-PFT study, and about 2% in the FREEDOM study had received prior hormone replacement therapy. The HORIZON-PFT and FREEDOM studies also included patients previously treated with bisphosphonates (15% and 13%, respectively) or selective oestrogen receptor modulator (SERMS) (11% and 2%, respectively). However, none of the 5 studies provided information on the duration of prior treatment.

The study drop-out rates were comparable (13% to 17%). Information on the number of participants with early discontinuation of treatment with the study medication was available only for the FREEDOM study (about 7%).

### 4.2.2 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 3 studies as well as from 2 studies added in the sensitivity analysis. Table 4 presents an overview of the data available on patient-relevant outcomes from the included studies.

In the FREEDOM and HORIZON-PFT studies, data were reported on all patient-relevant outcomes except symptomatic atypical femoral fractures. In the DIRECT study, data were reported only for the outcome of all-cause mortality, fractures in the hip area, nonvertebral symptomatic fractures, and side effects outcomes. Regarding AEs of the gastrointestinal tract, the DIRECT study reported results for individual Preferred Terms (PTs), but these do not adequately reflect the System Organ Class (SOC) AEs of the gastrointestinal tract and were therefore unusable for the present benefit assessment.

No indirect comparison was possible for the outcomes of pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, or symptomatic atypical femoral fractures. This is explained below.

The FREEDOM and HORIZON-PFT studies used different instruments (FREEDOM: OPAQ-SV; HORIZON-PFT: mini-OQLQ) for surveying health-related quality of life. The instruments' structure (type and analysis of the surveyed domains) was insufficiently comparable. No summary analysis can be conducted for the individual questions. A comparison

of individual subscales is likewise impossible due to excessive differences in the questions. An analysis of a total score is not available for the mini-OQLQ (HORIZON-PFT study) and was not envisaged for the OPAQ-SV instrument (FREEDOM study). Regardless of the vitality check for these instruments, no indirect comparison was therefore possible for the outcome of health-related quality of life. For the outcome of symptomatic atypical femoral fractures, no results suitable for an indirect comparison were available because this outcome was not surveyed in the HORIZON-PFT study, and consequently, data were not available on both sides of the indirect comparison. The outcomes of pain and functional limitations were surveyed in the FREEDOM and HORIZON-PFT studies by asking patients different questions on back pain and limitations due to back pain (FREEDOM study: Back Pain and Limited Activity Days Questionnaire; HORIZON-PFT: Quarterly Back Pain Questionnaire). Neither the outcomes of pain and functional limitations nor the outcome of osteonecrosis of the jaw were associated with the certainty of results required for performing an indirect comparison (see Section 4.2.3).

The MK0217-035 and MK0217-037 studies, which were added in a sensitivity analysis, reported data usable in the benefit assessment or allowed an indirect comparison only for the outcomes of all-cause mortality, SAEs, and discontinuation due to AEs. No other patient-relevant outcomes were surveyed in the MK0217-035 and MK0217-037 studies, or no usable data were available for the outcome of AEs of the gastrointestinal tract.

Table 4: Matrix of patient-relevant outcomes (indirect comparison: denosumab versus zoledronate or denosumab versus zoledronate and alendronate)

| Study | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Fractures[a] | | | | | | | | | | | |
| | All-cause mortality | Fractures in the hip area | Distal radius fractures | Symptomatic vertebral fractures | Nonvertebral symptomatic fractures | Pain | Functional limitations | Health-related quality of life | SAEs | Discontinuation due to AEs | Osteonecrosis of the jaw | Symptomatic atypical femoral fractures | AEs of the gastrointestinal tract (SOC, AEs, and SAEs) |
| **Denosumab** | | | | | | | | | | | | | |
| DIRECT | ● | ● | – | –[b] | ● | – | – | – | ● | ● | ● | ● | ○[c] |
| FREEDOM | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | – | ● |
| **Bisphosphonates, zoledronate** | | | | | | | | | | | | | |
| HORIZON-PFT | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | – | ● |
| **Indirect comparison possible[d]** | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | No | No | Yes |
| **Supplementary sensitivity analysis (addition of studies whose participants were at moderate fracture risk)** | | | | | | | | | | | | | |
| **Bisphosphonates, alendronate** | | | | | | | | | | | | | |
| **MK0217-035** | ● | – | – | – | – | – | – | – | ● | ● | – | – | ○[e] |
| **MK0217-037** | ● | – | – | – | – | – | – | – | ● | ● | – | – | ○[e] |
| **Indirect comparison possible in the sensitivity analysis[d]** | Yes | No | No | No | No | No | No | No | Yes | Yes | No | No | No |

a. For the present benefit assessment, fracture outcomes are used if they were surveyed as effectiveness outcomes using an adequate operationalization. Results on fractures which were reported in the AE/SAE analysis, e.g. as individual PTs, are disregarded because, firstly, it is unclear whether said fractures were low-trauma fractures typical for osteoporosis. Secondly, the analysis in the context of AEs/SAEs is insufficiently comparable to a clearly defined and systematic survey of fractures as an effectiveness outcome. Table 59 of the full report showing study characteristics provides information on the studies in which fractures were analysed as AEs/SAEs.
b. Vertebral fractures were surveyed, but not separately as symptomatic vertebral fractures.
c. Only events from individual PTs were reported, but not results on the SOC of gastrointestinal disorders (MedDRA coded).
d. See discussion in the body of the text regarding the reasons for unfeasibility.
e. For the AE survey, a coding system other than MedDRA coding was used. The events recorded using this coding system do not fully reflect the SOC of gastrointestinal disorders (MedDRA coded) according to the operationalization of the outcome.
●: outcome was recorded
○: data were reported but were unusable on the study level: see information provided in the corresponding footnotes
–: outcome not recorded

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class

### 4.2.3 Assessment of the risk of bias of the results

The risk of bias across outcomes was rated as low for the FREEDOM and HORIZON-PFT studies and as high for the DIRECT study. In the DIRECT and HORIZON-PFT studies, the generation of the randomization sequence was unclear. Additionally, allocation concealment was unclear in the DIRECT study.

Based on the high risk of bias at study level, the outcome-specific risk of bias was rated as high for the results of the outcomes reported in the DIRECT study. The risk of bias of results was rated as low for all reported outcomes except for pain and functional limitations in the FREEDOM and HORIZON-PET studies and except for osteonecroses in the HORIZON-PET study. For the FREEDOM and HORIZON-PFT studies' outcomes of pain and functional limitations, the high risk of bias was due to a high percentage of study dropouts as well as a lack of information on whether and how missing values were replaced (FREEDOM study) or which percentage of participants had missing information at the respective measuring time point (HORIZON-PFT study). The high risk of bias of the osteonecrosis of the jaw outcome in the HORIZON-PFT study is due to the fact that the analysis of this outcome was not pre-specified.

Where only 1 study was available on one edge of an indirect comparison and results of individual outcomes from this study were associated with a high risk of bias, the certainty of results necessary to conduct an adjusted indirect comparison was insufficient. For the outcomes of pain, functional limitations, and osteonecrosis of the jaw, no results of sufficient certainty were therefore available for an adjusted indirect comparison.

**Supplementary sensitivity analysis: addition of studies whose participants were at moderate fracture risk**

For the MK0217-035 and MK0217-037 studies, which were added in a sensitivity analysis, the risk of bias across outcomes was rated as high.

For the MK0217-035 and MK0217-037 studies, the risk of bias of results for the outcomes of all-cause mortality, SAEs, and discontinuation due to AEs was rated as high due to the high risk of bias across outcomes. Other patient-relevant outcomes were not surveyed in the studies, or no usable data were available.

### 4.2.4 Results on patient-relevant outcomes

**Maximum possible strength of evidence given the available data**

On the basis of the available information for the outcome of all-cause mortality as well as the outcomes of the fractures and side effects categories, it was possible to derive at most hints, e.g. of greater benefit.

**Time points taken into account**

The studies reported results either after 2 years or after 3 years. The 2 time points were deemed sufficiently similar and used for the present benefit assessment.

**Subgroup characteristics and other effect modifiers**

Only 2 of the 3 studies (FREEDOM, HORIZON-PFT) provided analyses on subgroups and other effect modifiers. For outcomes on which an indirect comparison of denosumab versus bisphosphonates was possible, however, overlapping subgroup analyses were reported for both studies and available for the benefit assessment only regarding the outcome of fractures in the hip area for the subgroup characteristics of age or BMD (T-score) at the femoral neck. No effect modification was found for the characteristic of BMD (T-score) of the femoral neck. For the characteristic of age, the indirect comparison of denosumab versus zoledronate showed a statistically significant interaction, but the effects in the subgroups were not statistically significant.

In the MK0217-035 and MK0217-037 studies, which were added in a supplementary sensitivity analysis, subgroup analyses had been planned, but no results were reported on the outcomes which are patient relevant for the present benefit assessment.

Overall, no effect modifications are found for the comparison of denosumab versus bisphosphonates which was investigated in the present benefit assessment.

**Results of the comparison of denosumab versus bisphosphonates**

Table 5 shows the results of the comparison of denosumab versus zoledronate and the comparison of denosumab versus zoledronate and alendronate (supplementary sensitivity analysis). Detailed information on the study results are found in Section A3.3.2 of the full report.

Table 5: Comparison of denosumab versus bisphosphonates, overview of effects with regard to the patient-relevant outcomes (multipage table)

| **Outcome category**<br>**Outcome** | **Indirect comparison via common comparators** | |
|---|---|---|
| | **Denosumab versus zoledronate**<br>**Effect estimation [95% CI]; p-value** | **Denosumab versus zoledronate and alendronate (supplementary sensitivity analysis)**<br>**Effect estimation [95% CI]; p-value** |
| **Mortality** | | |
| All-cause mortality | RR: 0.68 [0.46; 1.01]; p = 0.054 | RR: 0.60 [0.13; 2.82]; p = 0.515 |
| **Morbidity** | | |
| fractures in the hip area | HR: 0.99 [0.55; 1.78]; p = 0.974 | - |
| Distal radius fractures[a] | Forearm fractures: HR: 1.05 [0.72; 1.52]; p = 0.800<br>Wrist fractures: HR: 1.04 [0.70; 1.53]; 0.855 | - |
| Symptomatic vertebral fractures | HR: 1.35 [0.71; 2.57]; p = 0.366 | - |
| Nonvertebral symptomatic fractures[b] | HR: 1.08 [0.86; 1.36]; p = 0.496 | - |
| Pain | - | - |
| Functional limitations | - | - |
| **Health-related quality of life** | - | - |
| **Side effects** | | |
| SAEs | RR: 1.06 [0.96; 1.17]; p = 0.256 | RR: 1.22 [0.69; 2.15]; p = 0.490 |
| Discontinuation due to AEs | RR: 0.83 [0.64; 1.08]; p = 0.158 | RR: 0.85 [0.66; 1.09]; p = 0.198 |
| Osteonecrosis of the jaw | - | - |
| Symptomatic atypical femoral fractures | - | - |
| AEs of the gastrointestinal tract (SOC) | | |
| AEs | RR: 0.94 [0.86; 1.02]; p = 0.134 | - |
| SAEs | RR: 1.33 [0.95; 1.85]; p = 0.093 | - |

Table 5: Comparison of denosumab versus bisphosphonates, overview of effects with regard to the patient-relevant outcomes (multipage table)

| **Outcome category** | **Indirect comparison via common comparators** | |
|---|---|---|
| **Outcome** | **Denosumab versus zoledronate**<br><br>**Effect estimation [95% CI]; p-value** | **Denosumab versus zoledronate and alendronate (supplementary sensitivity analysis)**<br><br>**Effect estimation [95% CI]; p-value** |
| a. The studies did not provide a specific operationalization for the outcome of distal radius fractures. For the outcome of distal radius fractures, both possible operationalizations ("forearm fractures" and "wrist fractures") were taken into account.<br>b. For this outcome, nonvertebral fracture events which are presumably symptomatic or clinical nonvertebral fractures were used (see Section A3.3.2.6 of the full report).<br>-: no (usable) data reported for the indirect comparison; see discussion in Sections 4.2.2 and 4.2.3<br>AE: adverse event; CI: confidence interval; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class | | |

The alendronate studies MK0217-035 and MK0217-037 each have low case numbers and event rates in comparison with the zoledronate study HORIZON-PFT. In the metaanalytical summary assuming a model with random effects, these 2 studies are weighted disproportionately high. Overall, this leads to a highly imprecise estimate on the bisphosphonate(s) edge. Hence, the sensitivity analysis is to be deemed non-informative and cannot be used for the weighing of benefit versus harm of denosumab versus zoledronate and alendronate. Conclusions on the benefit and harm of denosumab can be drawn only in comparison with zoledronate. However, the results of the sensitivity analysis are presented as supplementary information.

No statistically significant differences between treatment groups were found or no (usable) data were reported for the patient-relevant outcomes. This results in no hint of greater or lesser benefit or harm of denosumab in comparison with zoledronate for any of the outcomes.

### 4.2.5 Summarizing assessment of the results

**Evidence map**

Table 6 below shows the evidence map regarding patient-relevant outcomes for the comparison of denosumab versus bisphosphonates.

Table 6: Comparison of denosumab versus bisphosphonates; evidence map with regard to patient-relevant outcomes

| | All-cause mortality | Fractures | | | | Pain | Functional limitations | Health-related quality of life | SAEs | Discontinuation due to AEs | Osteonecrosis of the jaw | Symptomatic atypical femoral fractures | AEs of the gastrointestinal tract (SOC, AEs and SAEs) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Fractures in the hip area | Distal radius fractures[a] | Symptomatic vertebral fractures | Nonvertebral symptomatic fractures | | | | | | | | AEs | SAEs |
| **Denosumab versus zoledronate[b]** | ⇔ | ⇔ | ⇔ | ⇔ | ⇔ | -[c] | -[c] | -[d] | ⇔ | ⇔ | -[c] | -[e] | ⇔ | ⇔ |

a. The 2 possible operationalizations "forearm fractures" and "wrist fractures" were taken into account (see Table 30 of the full report).
b. Given the available evidence, conclusions on the benefit or harm associated with denosumab can be drawn only in comparison with zoledronate (see discussion in text).
c. The prerequisites for drawing conclusions of sufficient certainty of results regarding benefit or harm from an adjusted indirect comparison were not met.
d. The studies used different instruments for measuring health-related quality of life (FREEDOM: OPAQ-SV; HORIZON-PFT: mini-OQLQ). The instruments' structure (type and analysis of the surveyed domains) was insufficiently comparable. Therefore, no indirect comparison is possible. Hence, no check of validity of the individual instruments was performed.
e. For this outcome, none of the results are suitable for the indirect comparison because data are not available on both sides of the indirect comparison.
⇔: no hint of greater or lesser benefit or harm from denosumab versus zoledronate
-: no data reported for the indirect comparison

AE: adverse event; mini-OQLQ: mini Osteoporosis Quality of Life Questionnaire; OPAQ-SV: Osteoporosis Assessment Questionnaire Short Version; SAE: serious adverse event; SOC: System Organ Class

**Assessment of the volume of unpublished data**

No relevant study without reported results has been found (see Section A3.1.4 of the full report). Therefore, this aspect did not reduce the certainty of results in the present benefit assessment.

As described in Section 4.1, the data transmitted by the manufacturer were incomplete for risedronate. Publication bias is likely for the intervention of risedronate. Consequently, no proof, indication, or hint of benefit or harm is derived for the intervention of risedronate (except for a hint of lesser benefit from the comparison of teriparatide versus risedronate; see Section 4.3.5).

**Weighing of benefits versus harm**

For the comparison of denosumab versus zoledronate (main analysis), no hint of greater or lesser benefit or harm was found for any of the outcomes.

In the comparison of denosumab versus bisphosphonates, conclusions on the available evidence could be drawn only for the comparison of denosumab versus zoledronate on the basis of studies with patients at high fracture risk. This is due, firstly, to studies for a comparison with denosumab not being available for all bisphosphonates. Due to their disproportionately high weight (despite low case numbers and, in some cases, lower event rates), the alendronate studies which were additionally included in a sensitivity analysis led to a highly imprecise estimate on the bisphosphonate(s) edge in the metaanalyses. Hence, the sensitivity analysis was to be deemed non-informative. Secondly, for the comparison of the bisphosphonates with each other (see Section 4.4.5), relevant studies were available not for all bisphosphonates, but only for the comparison of alendronate versus ibandronate, and the studies were based on low case numbers. Overall, while the available data do not call into question a joint analysis of bisphosphonates, they are insufficient for evaluating bisphosphonates as a group.

Overall, across outcomes, there is no hint of greater or lesser benefit or harm from denosumab versus zoledronate.

## 4.3 Comparison of teriparatide versus risedronate

Given the available evidence, the study pool for investigating teriparatide versus risedronate comprises 1 study with patients at high fracture risk (see Table 19 and Table 20 in Section A3.2 of the full report) for which data are in principle available for a comparison of teriparatide versus risedronate.

### 4.3.1 Characteristics of the studies included in the assessment

**Study design**

The VERO [199] study is a double-blind, multicentre RCT. The study started in 2012, and its treatment duration was 2 years.

The VERO study investigates the intervention of teriparatide versus risedronate. The study enrolled a total of 1360 patients, who were randomized in a 1:1 ratio either to treatment with teriparatide (20 µg/day) or risedronate (35 mg/week).

Vertebral fractures were investigated as the primary outcome of the study. Secondary patient-relevant outcomes surveyed in the study were pain and side effects.

**Study population**

The mean participant age in the VERO study was about 73 years. Almost all participants were of Caucasian descent.

Over 90% of participants had existing fractures. Overall, about one-fourth of participants had 1 existing fracture, and another one-fourth had 2. About 86% of participants had vertebral fractures, while about 43% had nonvertebral fractures. Regarding other fracture risk factors, data were available only on body weight, height, BMI, and the percentage of participants with existing fractures. The average participant weighed 65 kg, was 155 cm in height, and had a BMI of approximately 27 kg/m$^2$. VERO participants had a mean BMD (T-score) of -2.3 at both the femoral neck and at the lumbar spine.

Nearly 60% of participants had received prior treatment with bisphosphonates, and ≤ 4% of participants each with denosumab, SERM, and hormones. On average, prior treatment had been administered for 4.5 years.

About one-fourth of VERO participants dropped out of the study.

### 4.3.2 Overview of patient-relevant outcomes

Table 7 shows an overview of the data available on patient-relevant outcomes from the included VERO study. The data on the outcomes of all-cause mortality, fractures in the hip area, distal radius fractures, symptomatic vertebral fractures, nonvertebral symptomatic fractures, pain, and side effects were reported and were usable. No data were available for the outcomes of functional limitations and health-related quality of life.

Table 7: Matrix of patient-relevant outcomes (direct comparison: teriparatide versus risedronate)

| Study | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Fractures[a] | | | | | | | | | | | |
| | All-cause mortality | Fractures in the hip area | Distal radius fractures | Symptomatic vertebral fractures | Nonvertebral symptomatic fractures | Pain | Functional limitations | Health-related quality of life | SAEs | Discontinuation due to AEs | Osteonecrosis of the jaw | Symptomatic atypical femoral fractures | AEs of the gastrointestinal tract (SOC, AEs and SAEs) |
| VERO | ● | ● | ● | ● | ● | ● | – | – | ● | ● | ● | ● | ● |

a. For the present benefit assessment, fracture outcomes are used if they were surveyed as effectiveness outcomes using an adequate operationalization.
●: outcome was recorded
–: outcome not recorded
AE: adverse event; SAE: serious adverse event; SOC: System Organ Class

### 4.3.3 Assessment of the risk of bias of the results

The risk of bias at the study level was rated as low for the VERO study.

For all outcomes reported in the VERO study, the risk of bias of results was rated as high. In all outcomes except pain, this is due to the high percentage of study drop-outs. For the outcome of pain, the high risk of bias is due to a large percentage of participants who were not fully entered into the analysis. The outcomes of functional limitations and health-related quality of life were not surveyed in the VERO study.

### 4.3.4 Results on patient-relevant outcomes

**Maximum possible strength of evidence given the available data**

The available data resting on 1 study lent themselves to derive at most hints of greater or lesser benefit or harm for all outcomes.

**Time points taken into account**

For the VERO study, results were reported after 2 years. These results were used for the present benefit assessment.

**Subgroup characteristics and other effect modifiers**

For the VERO study, analyses on subgroup characteristics and other effect modifiers were available, but only on the outcome of nonvertebral symptomatic fractures, which is patient-relevant for the present benefit assessment. No statistically significant interaction was found for this outcome. For other patient-relevant outcomes, an investigation of subgroup characteristics and other effect modifiers was not possible.

**Results on the comparison of teriparatide versus risedronate**

Table 8 shows the results of the comparison of teriparatide versus risedronate. Detailed information on the study results are found in Section A3.4.2 of the full report.

Table 8: Comparison of teriparatide versus risedronate; overview of effects with regard to patient-relevant outcomes

| **Outcome category**<br>**Outcome** | **Direct comparison of teriparatide versus risedronate**<br>**VERO**<br>**Effect estimation [95% CI];**<br>**p-value** |
|---|---|
| **Mortality** | |
| All-cause mortality | RR: 2.14 [0.88; 5.22];<br>p = 0.097 |
| **Morbidity** | |
| Fractures in the hip area | RR: 0.40 [0.08; 2.05][a];<br>p = 0.290 |
| Distal radius fractures[b] | RR: 0.60 [0.22; 1.64];<br>p = 0.331 |
| Symptomatic vertebral fractures | HR: 0.284 [0.14; 0.58];<br>p = 0.002 |
| Nonvertebral symptomatic fractures[c] | HR: 0.66 [0.39; 1.10];<br>p = 0.099 |
| Pain[d] | MD: -0.08 [-0.30; 0.14];<br>p = 0.478 |
| Functional limitations | - |
| **Health-related quality of life** | - |
| **Side effects** | |
| SAEs | RR: 1.19 [0.95; 1.49];<br>p = 0.129 |
| Discontinuation due to AEs | RR: 1.40 [0.98; 1.99];<br>p = 0.070 |
| Osteonecrosis of the jaw | RR: not calculable[e] |
| Symptomatic atypical femoral fractures | RR: not calculable[e] |
| AEs of the gastrointestinal tract (SOC)<br>AEs | <br>RR: 1.26 [1.01; 1.57];<br>p = 0.040 |
| SAEs | RR: 1.44 [0.62; 3.36];<br>p = 0.530 |

a. The 95% confidence interval for relative effect is so imprecise that neither an effect being cut in half nor one being doubled can be ruled out.
b. A specific operationalization for the outcome of distal radius fractures was not available in the study. For the outcome of distal radius fractures, the radius fractures events were used.
c. The results on nonvertebral fractures which are presumably symptomatic was used for this outcome.
d. Surveyed as back pain, measured by a numeric rating scale (NRS) from 0 (no back pain) to 10 (worst imaginable back pain).
e. No events occurred in either study arm.
-: no data reported; see discussion in Section 4.3.2

AE: adverse event; CI: confidence interval; HR: hazard ratio; MD: mean difference; NRS: numerical rating scale; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Regarding the outcome of symptomatic vertebral fractures, there was a favourable effect for teriparatide versus risedronate. For symptomatic vertebral fractures, this results in a hint of greater benefit of teriparatide in comparison with risedronate.

Regarding the outcome of AEs of the gastrointestinal tract, there was an unfavourable effect for teriparatide versus risedronate. For symptomatic AEs of the gastrointestinal tract, this results in a hint of greater harm from teriparatide in comparison with risedronate.

There were no other favourable or unfavourable effects of teriparatide versus risedronate. Consequently, there was no hint of greater or lesser benefit or harm for the other patient-relevant outcomes.

### 4.3.5 Summarizing assessment of the results

**Evidence map**

The following Table 9 shows the evidence map regarding patient-relevant outcomes for the comparison of teriparatide versus risedronate.

Table 9: Comparison of teriparatide versus risedronate; evidence map regarding the patient-relevant outcomes

| | All-cause mortality | Fractures | | | | Pain | Functional limitations | Health-related quality of life | SAEs | Discontinuation due to AEs | Osteonecrosis of the jaw | Symptomatic atypical femoral fractures | AEs of the gastrointestinal tract (SOC, AEs and SAEs) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Fractures in the hip area | Distal radius fractures | Symptomatic vertebral fractures | Nonvertebral symptomatic fractures | | | | | | | | AEs | SAEs |
| **Teriparatide versus risedronate** | ⇔ | (⇔) | ⇔ | ⇗ | ⇔ | ⇔ | -[a] | -[a] | ⇔ | ⇔ | ⇔ | ⇔ | ⇘ | ⇔ |

a. Outcome not recorded.
⇗: hint of greater benefit of teriparatide versus risedronate
⇗: hint of greater harm from teriparatide versus risedronate
⇔: no hint of greater or lesser benefit or harm from teriparatide versus risedronate
(⇔): no hint; the 95% confidence interval for relative effect is so imprecise that neither halving nor doubling of effect can be ruled out
-: no data reported

AE: adverse event; SAE: serious adverse event; SOC: System Organ Class

**Assessment of the volume of unpublished data**

No relevant study without reported results has been found (see Section A3.1.4 of the full report). Therefore, this aspect did not reduce the certainty of results in the present benefit assessment.

As described in Section 4.1, the data transmitted by the manufacturer were incomplete for risedronate. In the comparison of teriparatide versus risedronate, the incompleteness of the manufacturer documents was irrelevant because all studies were available on this comparison.

**Weighing of benefits versus harm**

Overall, the favourable effect for teriparatide in comparison with risedronate in the outcome of symptomatic vertebral fractures is therefore contrasted by an unfavourable effect for teriparatide in comparison with risedronate in the outcome of AEs of the gastrointestinal tract. Given the fact that a substantial effect in favour of teriparatide was found for the outcome of symptomatic vertebral fractures (upper limit of the 95% confidence interval: 0.58), while the disadvantage in the outcome of AEs of the gastrointestinal tract was marginal (95% confidence interval: [1.01; 1.57]) and was not found in the SAEs of the gastrointestinal tract, the overall evaluation of benefit and harm across outcomes derived a hint of greater benefit of teriparatide versus risedronate.

## 4.4 Bisphosphonates in comparison with each other

Given the available data, the study pool for comparing bisphosphonates with each other consists of 6 studies with patients at low fracture risk (MK0217-037, -041, -063, Bai 2013, Guanabens 2013) or moderate fracture risk (TRIO study; see Table 19 und Table 20 in Section A3.2 of the full report), for which data for comparing bisphosphonates with each other were in principle available.

As described in Section 4.1, the 4 studies whose participants were at low fracture risk allowed performing an adjusted indirect comparison of alendronate (MK0217-037, -041, -063 study) versus zoledronate (Bai 2013 study) via the common comparator of placebo. However, the adjusted indirect comparison was foregone due to the studies' missing data. Only the outcome of SAEs was surveyed on both edges of the comparison (see Table 71 in Section A10 of the full report). The Bai 2013 study (only study on the zoledronate-placebo edge) either did not survey any benefit outcomes relevant for the present benefit assessment or no usable data were available. Hence, it is impossible to weigh benefit and harm. Furthermore, the sensitivity analysis already investigated the outcome of SAEs for the comparison of denosumab versus bisphosphonates, specifically for the bisphosphonates of zoledronate and alendronate (see Table 5 in Section 4.2.4). Data from an indirect comparison of the MK0217-037, -041, -063, and Bai 2013 studies are not expected to call into question this result on SAEs. The Bai 2013, MK0217-037, MK0217-041, and MK0217-063 studies were therefore not further investigated for the comparison of bisphosphonates with each other.

As described in Section 4.1, the studies Guanabens 2013 (alendronate versus ibandronate) and TRIO (alendronate versus ibandronate versus risedronate), for which participants' fracture risk was deemed low (Guanabens 2013) or moderate (TRIO), allowed a direct comparison of the bisphosphonates alendronate versus ibandronate in the form of a potential metaanalysis. This analysis disregarded the additional risedronate arm of the TRIO study. This arm is not presented below.

The Guanabens 2013 and TRIO studies and their available results are described below.

### 4.4.1 Characteristics of the studies included in the assessment

**Study design**

The Guanabens 2013 [128] and TRIO [194] studies were performed as open-label RCTs. The Guanabens 2013 study was monocentric (Spain), while the TRIO study was performed in the United Kingdom. The studies' treatment duration was 2 years, with each study starting in 2007.

Both studies examined the intervention of alendronate (70 mg/week) versus ibandronate (150 mg/month). The TRIO study additionally had a risedronate arm (35 mg/week). As described above, the risedronate arm of the TRIO study is irrelevant for the present benefit assessment and is disregarded below.

At 114 participants (in the study arms relevant for the present benefit assessment), the TRIO study comprises a larger patient population than the Guanabens 2013 study, which included a total of 42 participants.

The primary outcome of the TRIO study was the calcaneus stiffness index. Further patient-relevant outcomes investigated in the TRIO study include outcomes of fractures and side effects. The Guanabens 2013 study investigated BMD (lumbar spine, proximal femur) and fracture and side effects outcomes.

**Study populations**

The Guanabens 2013 and TRIO studies had a mean participant age of 65 and 68, respectively. Neither of the studies provided any information on participant ancestry.

The fracture risk factor of BMI was reported in both studies and was comparable between the studies (mean BMI: 26.6 and 26.2 $kg/m^2$, respectively). Information on participants' mean bodyweight (67 kg) and height (160 cm) was available only for the TRIO study, however.

Both studies provided data on lumbar spine BMD. Guanabens 2013 participants exhibited a mean T-score of -2.6, while TRIO participants had a mean T-score of -2.3. Femoral neck BMD was reported only by the Guanabens 2013 study (mean T-score: -1.8).

Unlike the TRIO study, the Guanabens 2013 study reported information on the percentage of participants with existing fractures (alendronate: 59%; ibandronate: 25%). Both studies

reported data, albeit few, on the specific localization of existing fractures. Only the TRIO study provided data on participants with existing hip fractures (alendronate: 3.5%; ibandronate: 1.8%), while only the Guanabens 2013 study reported on patients with existing nonvertebral fractures (alendronate: 45%; ibandronate: 20%). The only information available from both studies was the percentage of participants with existing vertebral fractures. It showed that 18% to 23% of participants had vertebral fractures, with the TRIO study's ibandronate arm coming in at only 9%.

While TRIO participants exhibited no concomitant disease or therapies affecting fracture risk, all Guanabens 2013 participants had primary biliary cholangitis. Data on prior treatment were available only for the TRIO study, In this study, virtually all patients had received no prior treatment.

Overall, study drop-out was more common in TRIO participants (about 45%) than in Guanabens 2013 participants (about 21%).

### 4.4.2 Overview of patient-relevant outcomes

Table 10 presents an overview of the data available on patient-relevant outcomes from the included studies. Only on the SAEs outcome were data reported by both studies and usable for the benefit assessment. Results on the outcomes of fractures as well as discontinuation due to AEs were reported only for the Guanabens 2013 study, while AEs of the gastrointestinal tract were reported only for the TRIO study. The Guanabens 2013 study reported no data on the outcome of all-cause mortality despite its methods discussing this survey. None of the studies reported data on the outcomes of pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, and symptomatic atypical femoral fractures.

Table 10: Matrix of patient-relevant outcomes (direct comparison: alendronate versus ibandronate)

| Study | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Fractures[a] | | | | | | | | | | | |
| | All-cause mortality | Fractures in the hip area | Distal radius fractures | Symptomatic vertebral fractures | Nonvertebral symptomatic fractures | Pain | Functional limitations | Health-related quality of life | SAEs | Discontinuation due to AEs | Osteonecrosis of the jaw | Symptomatic atypical femoral fractures | AEs of the gastrointestinal tract (SOC, AEs and SAEs) |
| Guanabens 2013 | x | ● | ● | –[b] | ● | – | – | – | ● | ● | – | – | – |
| TRIO | – | – | – | – | – | – | – | – | ● | – | – | – | ● |

a. For the present benefit assessment, fracture outcomes are used if they were surveyed as effectiveness outcomes using an adequate operationalization. Results on fractures which were reported in the AE/SAE analysis, e.g. as individual PTs, are disregarded because, firstly, it is unclear whether said fractures were low-trauma fractures typical for osteoporosis. Secondly, the analysis in the context of AEs/SAEs is insufficiently comparable to a clearly defined and systematic survey of fractures as an effectiveness outcome. Table 59 of the full report showing study characteristics provides information on the studies in which fractures were analysed as AEs/SAEs.
b. Vertebral fractures were surveyed, but not separately as symptomatic vertebral fractures.
●: outcome was recorded
x: data were not reported despite the collection of these data being pre-specified
–: outcome not recorded
AE: adverse event; PT: preferred term; SAE: serious adverse event; SOC: System Organ Class

### 4.4.3 Assessment of the risk of bias of the results

The risk of bias across outcomes was rated as high for both Guanabens 2013 and TRIO. This was due to unclear allocation concealment as well as lack of blinding of participants (TRIO study) or the treatment provider (Guanabens 2013 study). In the Guanabens 2013 study, it was additionally unclear whether all pre-specified outcomes were fully reported because neither a study report nor a publication on the study design or study registry entry were available. In the TRIO study, the study arms were imbalanced with regard to pre-existing vertebral fractures at baseline (ibandronate 9% versus alendronate 23%). Due to delayed approval of the TRIO study duration, which was subsequently extended by 1 year, a high percentage of participants dropped out of the study after the end of the 1st phase (1 year) (27%). No justification was available for the subsequent doubling of the study duration.

For the outcomes surveyed or reported in the Guanabens 2013 and TRIO studies, the outcome-specific risk of bias was rated as high due to the high risk of bias on the study level.

### 4.4.4 Results on patient-relevant outcomes

**Maximum possible strength of evidence given the available data**

On the basis of the available information, it was possible to derive at most indications, e.g. of greater benefit, for outcomes of the fractures and side effects categories.

**Time points taken into account**

For the Guanabens 2013 and TRIO studies, results after 2 years were reported. These results were used for the present benefit assessment.

**Subgroup characteristics and other effect modifiers**

In the Guanabens 2013 and TRIO studies, analyses of subgroups or other effect modifiers were not available for any of the outcomes which are patient relevant for the present benefit assessment. Given the available evidence, it is impossible to investigate potential effect modifiers for the comparison of different bisphosphonates with each other.

**Results of the comparison of different bisphosphonates with each other**

Table 11 shows the results of the comparison of different bisphosphonates with each other Detailed information on the study results are found in Section A3.5.2 of the full report.

Table 11: Comparison of different bisphosphonates with each other; overview of effects with regard to the patient-relevant outcomes

| **Outcome category**<br>**Outcome** | **Direct comparison of alendronate versus ibandronate** | |
|---|---|---|
| | **Guanabens 2013**<br>**Effect estimation [95% CI]; p-value** | **TRIO**<br>**Effect estimation [95% CI]; p-value** |
| **Mortality** | | |
| All-cause mortality | - | - |
| **Morbidity** | | |
| Fractures in the hip area[a] | RR: not calculable[b] | - |
| Distal radius fractures[a] | RR: not calculable[b] | - |
| Symptomatic vertebral fractures | - | - |
| Nonvertebral symptomatic fractures[a] | RR: not calculable[b] | - |
| Pain | - | - |
| Functional limitations | - | - |
| **Health-related quality of life** | - | - |
| **Side effects** | | |
| SAEs[c] | RR: not calculable[b] | RR: 0.29 [0.06; 1.32]; p = 0.095 |
| Discontinuation due to AEs | RR: 0.81 [0.09; 2.22][d]; p = 0.358 | - |
| Osteonecrosis of the jaw | - | - |
| Symptomatic atypical femoral fractures | - | - |
| AEs of the gastrointestinal tract (SOC)<br>AEs | - | RR: 1.29 [0.83; 1.99]; p = 0.279 |
| SAEs | - | RR: 0.14 [0.01; 2.70][d]; p = 0.093 |

a. The studies did not offer a specific operationalization for this outcome. The information available on the Guanabens 2013 study show that, overall, no nonvertebral fractures occurred.
b. No events occurred in either study arm.
c. No meta-analysis was performed because in 1 of 2 studies, no event occurred.
d. The 95% confidence interval for relative effect is so imprecise that neither an effect being cut in half nor one being doubled can be ruled out.
-: no data reported; see discussion in Section 4.4.2

AE: adverse event; CI: confidence interval; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

No statistically significant differences between treatment groups were found or no (usable) data were reported for the patient-relevant outcomes. This results in no hint of greater or lesser benefit of alendronate in comparison with ibandronate for any of the outcomes.

### 4.4.5 Summarizing assessment of the results

**Evidence map**

The following Table 12 shows the evidence map regarding patient-relevant outcomes for the comparison of different bisphosphonates with each other.

Table 12: Comparison of different bisphosphonates with each other; evidence map with regard to patient-relevant outcomes

| | All-cause mortality | Fractures | | | | Pain | Functional limitations | Health-related quality of life | SAEs | Discontinuation due to AEs | Osteonecrosis of the jaw | Symptomatic atypical femoral fractures | AEs of the gastrointestinal tract (SOC, AEs and SAEs) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Fractures in the hip area | Distal radius fractures | Symptomatic vertebral fractures | Nonvertebral symptomatic fractures | | | | | | | | AEs | SAEs |
| **Alendronate versus ibandronate** | -[a] | ⇔ | ⇔ | -[a] | ⇔ | -[a] | -[a] | -[a] | ⇔ | (⇔) | -[a] | -[a] | ⇔ | (⇔) |

a. Outcome not recorded or, for the outcome of all-cause mortality, not reported despite its survey being pre-specified.
⇔: no hint of greater or lesser benefit or harm from alendronate versus ibandronate
(⇔): no hint; the 95% confidence interval for relative effect is so imprecise that neither halving nor doubling of effect can be ruled out
-: no data reported
AE: adverse event; SAE: serious adverse event; SOC: System Organ Class

**Assessment of the volume of unpublished data**

No relevant study without reported results has been found (see Section A3.1.4 of the full report). Therefore, this aspect did not reduce the certainty of results in the present benefit assessment.

As described in Section 4.1, the data transmitted by the manufacturer were incomplete for risedronate. Publication bias is likely for the intervention of risedronate. Consequently, no proof, indication, or hint of benefit or harm is derived for the intervention of risedronate (except for a hint of lesser benefit from the comparison of teriparatide versus risedronate; see Section 4.3.5).

**Weighing of benefits versus harm**

For the comparison between the bisphosphonates of alendronate versus ibandronate, no hint of greater or lesser benefit or harm was found in any of the outcomes.

While the available data show no signs of any differences between the bisphosphonates of alendronate and ibandronate, the data are insufficient for the bisphosphonates in the present benefit assessment to be generally regarded as an active substance group. This is due, firstly, to directly comparative data being available only for the comparison of the bisphosphonates alendronate versus ibandronate, which were further based on low patient numbers. Secondly, in the comparison of denosumab versus bisphosphonates, the alendronate studies led to a highly imprecise estimate and consequently to non-informative sensitivity analyses due to their disproportionately high weight in the metaanalyses of the studies with zoledronate or alendronate (despite low case numbers and, in some cases, low event rates). Hence, the analyses comparing the investigated bisphosphonates were unsuitable for establishing sufficient homogeneity or potential heterogeneity (see Section 4.2.5).

Overall, there is no hint of greater or lesser benefit or harm from alendronate versus ibandronate across outcomes. It must be noted that this overall conclusion rests on results from studies which enrolled few participants and, in some cases, exhibited very low event rates. All things considered, the absence of a hint of greater or lesser harm does not represent proof of the investigated drugs' equivalence.

# 5 Classification of the work result

As commissioned by the G-BA and in accordance with the report plan [209], the goal of the present benefit assessment was to investigate bisphosphonates, teriparatide, and denosumab in comparison with each other. The research question comprised an assessment of bisphosphonates in comparison with each other. At the time the G-BA commissioned the Institute, the bisphosphonates alendronate, ibandronate, risedronate, and zoledronate (including combinations with alfacalcidol, cholecalciferol, or calcium) were available in Germany for the treatment of postmenopausal osteoporosis.

Given the available data, it was impossible to create a complete network including all drugs. Instead, the individual comparisons possible based on the available data were analysed: (1) denosumab versus bisphosphonates, (2) teriparatide versus risedronate, and (3) bisphosphonates in comparison with each other.

The check for similarity verified that the included studies exhibit sufficient similarity, and in the process, studies with participants at high fracture risk were distinguished from those with participants at low or moderate fracture risk.

According to the report plan, bisphosphonates were to be viewed as therapeutically comparable and – unless assumptions on structural quality were blatantly violated – were to be analysed primarily as a node in a network (see Section A2.3.3 of the full report). While the available evidence does not call into question the joint analysis of bisphosphonates, it was overall insufficient for drawing general conclusions on bisphosphonates as a drug group. For some bisphosphonates, for instance, data for a comparison with denosumab or with teriparatide or for comparisons of bisphosphonates with each other were unavailable. In the comparison of bisphosphonates versus denosumab, only zoledronate (participants at high fracture risk) was available for analysis regarding patient-relevant outcomes. Due to their disproportionately high weight (despite low case numbers and, in some cases, lower event rates), the alendronate studies which were additionally included in a sensitivity analysis led to a highly imprecise estimate on the bisphosphonate(s) edge in the metaanalyses. Hence, the sensitivity analysis was to be deemed non-informative. Drawing conclusions on the benefit or harm of denosumab was possible only in comparison with zoledronate. For the comparison of different bisphosphonates with each other, data were likewise available only on the 2 bisphosphonates of alendronate and ibandronate, which further rested on low case numbers.

In addition, the manufacturer’s data transmission was incomplete for risedronate. Publication bias is likely for the intervention of risedronate. Consequently, no proof, indication, or hint of benefit or harm is derived for the intervention of risedronate (except for a hint of lesser benefit from the comparison of teriparatide versus risedronate; see explanation below).

However, the available data allowed comparing risedronate versus teriparatide. Since there was no connection to a network and all studies were available for the presentation of results on the comparison of teriparatide versus risedronate, the incompleteness of manufacturer documents

for risedronate is irrelevant in this case. For the direct comparison of teriparatide versus risedronate, the manufacturer documents were complete.

Overall, the available studies provide insufficient evidence. The insufficient data availability for assessing participants' fracture risk is problematic from a methodological and technical perspective. Consequently, it was impossible to check these studies for similarity regarding the key factor of fracture risk, and the studies in question therefore had to be disregarded in a potential network metaanalysis.

Due to poor data availability on patient-relevant outcomes, the description of the interventions' benefit and harm is limited in the studies used for the individual comparisons. The available evidence was insufficient, particularly for the outcomes of pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, and symptomatic atypical femoral fractures.

Regarding the outcomes of osteonecrosis of the jaw and symptomatic atypical femoral fractures, it must be noted that they represent side effects which are known to occur in bisphosphonates treatment but have not yet been described for teriparatide. Since in the analysed studies, such events did not occur under either drug, teriparatide or risedronate, there is no hint of greater or lesser harm from teriparatide versus risedronate. This does not prove equivalence of the investigated drugs with regard to the 2 outcomes. Nevertheless, osteonecrosis of the jaw and symptomatic atypical femoral fractures represent relevant treatment-related outcomes in the present therapeutic indication. Therefore, it is reasonable to compare bisphosphonates and the other drugs to be assessed for these outcomes in the present benefit assessment.

The overall limited amount of available evidence represents a general limitation for the present benefit assessment.

Notably, no studies were available which would have allowed a comparison of different treatment sequences. Given the available evidence, it was impossible to investigate these treatment strategies involving several drugs administered consecutively, which are gaining in importance due to the typically longer disease durations and the resulting long-term treatment [16].

# 6 Conclusion

Given the available evidence, the following individual comparisons were taken into account in the benefit assessment: denosumab versus bisphosphonates, teriparatide versus risedronate as well as bisphosphonates in comparison with each other.

For risedronate, the data transmission by the manufacturer was incomplete. Publication bias likely arose with respect to the risedronate intervention. Consequently, no proof, indication, or hint of benefit or harm is derived for the intervention of risedronate (except for a hint of lesser benefit from the comparison of teriparatide versus risedronate). In the comparison of teriparatide versus risedronate, the incompleteness of the manufacturer documents was irrelevant because all studies were available on this comparison.

The available evidence for patient-relevant outcomes is deemed limited overall. The available evidence was insufficient, particularly for the outcomes of pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, and symptomatic atypical femoral fractures.

**Comparison of denosumab versus bisphosphonates**

For the comparison of denosumab versus bisphosphonates, the available data allow drawing robust conclusions only in comparison with the drug zoledronate.

The evidence shows the following:

- No hint of greater benefit or harm resulted from the available data for the outcomes of all-cause mortality, fractures in the hip area, distal radius fractures, symptomatic vertebral fractures, nonvertebral symptomatic fractures, SAEs, discontinuation due to AEs as well as AEs and SAEs of the gastrointestinal tract.
- For the outcomes of pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, and symptomatic atypical femoral fractures, no data usable for the comparison of denosumab versus bisphosphonates were available; therefore, no hint of greater benefit or harm resulted for any of them.

In the overall weighing of benefit and harm, there was no hint of greater or lesser benefit or harm for treatment with denosumab in comparison with zoledronate across outcomes.

**Comparison of teriparatide versus risedronate**

For the comparison of teriparatide versus risedronate, which can be conducted given the available data, the evidence shows the following:

- For the outcome of symptomatic vertebral fractures, there was a hint of greater benefit of teriparatide versus risedronate.
- For the outcome of AEs of the gastrointestinal tract, there was a hint of greater harm from teriparatide versus risedronate.

- No hint of greater benefit or harm was found on the basis of the available data for the outcomes of all-cause mortality, fractures in the hip area, distal radius fractures, nonvertebral symptomatic fractures, pain, SAEs, discontinuation due to AEs, osteonecrosis of the jaw, and symptomatic atypical femoral fractures as well as SAEs of the gastrointestinal tract.
- No data were available for the outcomes of functional limitations or health-related quality of life; this resulted in no hint of greater harm or benefit.

Overall, the favourable effect for teriparatide in comparison with risedronate in the outcome of symptomatic vertebral fractures is therefore contrasted by an unfavourable effect for teriparatide in comparison with risedronate in the outcome of AEs of the gastrointestinal tract. Given the fact that the outcome of symptomatic vertebral fractures showed a substantial effect in favour of teriparatide (upper limit of the 95% confidence interval: 0.58), while the disadvantage was marginal in the outcome of AEs of the gastrointestinal tract (95% confidence interval: [1.01; 1.57]) and not present in SAEs of the gastrointestinal tract, the overall weighing of benefit and harm across outcomes resulted in a hint of greater benefit of teriparatide versus risedronate.

**Bisphosphonates in comparison with each other**

For the comparison of bisphosphonates with each other, robust conclusions based on the available data can be drawn only for the drugs of alendronate and ibandronate.

The evidence shows the following:

- No hint of greater benefit or harm was found based on the available data for the outcomes of fractures in the hip area, distal radius fractures, nonvertebral symptomatic fractures, SAEs, discontinuation due to AEs, or AEs and SAEs of the gastrointestinal tract.
- No data were available for the outcomes of all-cause mortality, symptomatic vertebral fractures, pain, functional limitations, health-related quality of life, osteonecrosis of the jaw, and symptomatic atypical femoral fractures; this resulted in no hint of greater benefit or harm for any of them.

In the overall weighing of benefit and harm, there was no hint of greater or lesser benefit or harm of alendronate versus ibandronate across outcomes.

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Please see full final report for full reference list.

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*The full report (German version) is published under*

*https://www.iqwig.de/en/projects/a19-10.html*

# Appendix A – Search strategies

## A.1 – Searches in bibliographic databases

### 1. MEDLINE

***Search interface: Ovid***

Ovid MEDLINE(R) 1946 to November Week 4 2019,

Ovid MEDLINE(R) Daily Update December 03, 2019

The following filters were adopted:

Systematic review: Wong [210] – High specificity strategy

RCT: Lefebvre [211] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)

| # | **Searches** |
|---|---|
| 1 | exp Osteoporosis/ |
| 2 | Bone Density/ |
| 3 | Osteoporotic Fractures/ |
| 4 | (osteoporosis or osteoporotic or osteopen*).ti,ab. |
| 5 | (bone* adj3 (densit* or loss* or mass* or fragility* or resorption* or turnover*)).ti,ab. |
| 6 | fracture*.ti. |
| 7 | or/1-6 |
| 8 | Female/ |
| 9 | women.ti,ab. |
| 10 | or/8-9 |
| 11 | (bisphosphonat* or alendronat* or ibandronat* or risedronat* or risedronic* or zoledronat* or zoledronic*).mp. |
| 12 | (teriparatid* or denosumab*).mp. |
| 13 | or/11-12 |
| 14 | and/7,10,13 |
| 15 | Randomized Controlled Trial.pt. |
| 16 | Controlled Clinical Trial.pt. |
| 17 | (randomized or placebo or randomly).ab. |
| 18 | Clinical Trials as Topic/ |
| 19 | trial.ti. |
| 20 | or/15-19 |
| 21 | exp Animals/ not Humans/ |
| 22 | 20 not 21 |
| 23 | and/14,22 |
| 24 | cochrane database of systematic reviews.jn. |
| 25 | (search or MEDLINE or systematic review).tw. |
| 26 | meta analysis.pt. |
| 27 | or/24-26 |
| 28 | and/7,13,27 |
| 29 | or/23,28 |
| 30 | 29 not (comment or editorial).pt. |
| 31 | 30 and (english or german).lg. |

***Search interface: Ovid***

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to December 03, 2019,

Ovid MEDLINE(R) Epub Ahead of Print December 03, 2019

| # | **Searches** |
|---|---|
| 1 | (osteoporosis or osteoporotic or osteopen*).ti,ab. |
| 2 | (bone* and (densit* or loss* or mass* or fragility* or resorption* or turnover*)).ti,ab. |
| 3 | fracture*.ti. |
| 4 | or/1-3 |
| 5 | women.ti,ab. |
| 6 | (bisphosphonat* or alendronat* or ibandronat* or risedronat* or risedronic* or zoledronat* or zoledronic*).mp. |
| 7 | (teriparatid* or denosumab*).mp. |
| 8 | or/6-7 |
| 9 | and/4-5,8 |
| 10 | (clinical trial* or random* or placebo).ti,ab. |
| 11 | trial.ti. |
| 12 | or/10-11 |
| 13 | and/9,12 |
| 14 | (search or meta analysis or medline or systematic review).ti,ab. |
| 15 | and/4,8,14 |
| 16 | or/13,15 |
| 17 | 16 not (comment or editorial).pt. |
| 18 | 17 and (english or german).lg. |

**2. Embase**

***Search interface: Ovid***

Embase 1974 to 2019 December 03

The following filters were adopted:

Systematic review: Wong [210] – High specificity strategy

RCT: Wong [210] – Strategy minimizing difference between sensitivity and specificity

| # | **Searches** |
|---|---|
| 1 | exp Osteoporosis/ |
| 2 | Bone Density/ |
| 3 | (osteoporosis or osteoporotic or osteopen*).ti,ab. |
| 4 | (bone* adj3 (densit* or loss* or mass* or fragility* or resorption* or turnover*)).ti,ab. |
| 5 | fracture*.ti. |
| 6 | or/1-5 |
| 7 | Female/ |
| 8 | women.ti,ab. |
| 9 | or/7-8 |
| 10 | (bisphosphonat* or alendronat* or ibandronat* or risedronat* or risedronic* or zoledronat* or zoledronic*).mp. |
| 11 | (teriparatid* or denosumab*).mp. |
| 12 | or/10-11 |
| 13 | and/6,9,12 |
| 14 | (random* or double-blind*).tw. |
| 15 | placebo*.mp. |
| 16 | or/14-15 |
| 17 | and/13,16 |
| 18 | (meta analysis or systematic review or MEDLINE).tw. |
| 19 | and/6,12,18 |
| 20 | or/17,19 |
| 21 | 20 not medline.cr. |
| 22 | 21 not (exp animal/ not exp human/) |
| 23 | 22 not (Conference Abstract or Conference Review or Editorial).pt. |
| 24 | 23 and (english or german).lg. |

**3. The Cochrane Library**

**Search interface: Wiley**

Cochrane Database of Systematic Reviews: Issue 12 of 12, December 2019

Cochrane Central Register of Controlled Trials: Issue 12 of 12, December 2019

| ID | Search |
|---|---|
| #1 | [mh "Osteoporosis"] |
| #2 | [mh ^"Bone Density"] |
| #3 | [mh ^"Osteoporotic Fractures"] |
| #4 | (osteoporosis or osteoporotic or osteopen*):ti,ab |
| #5 | (bone* NEAR/3 (densit* or loss* or mass* or fragility* or resorption* or turnover*)):ti,ab |
| #6 | fracture*:ti |
| #7 | #1 or #2 or #3 or #4 or #5 or #6 |
| #8 | [mh ^"Female"] |
| #9 | women:ti,ab |
| #10 | #8 or #9 |
| #11 | bisphosphonat* or alendronat* or ibandronat* or risedronat* or risedronic* or zoledronat* or zoledronic* |
| #12 | teriparatid* or denosumab* |
| #13 | #11 or #12 |
| #14 | #7 and #10 and #13 in Trials |
| #15 | #7 and #13 in Cochrane Reviews |

## A.2 – Searches in study registries

In "PharmNet.Bund Arzneimittel-Informationssystem" (drug information system), a search was carried out for entries with results reports on studies that had already been identified elsewhere.

**1. ClinicalTrials.gov**

***Provider: U.S. National Institutes of Health***

URL: http://www.clinicaltrials.gov

Type of search: Advanced Search

| Search strategy |
|---|
| ( bisphosphonate OR alendronate OR ibandronate OR risedronate OR zoledronate OR teriparatide OR denosumab ) AND AREA[ConditionSearch] ( osteoporosis OR osteopenia ) |

**2. EU Clinical Trials Register**

***Provider: European Medicines Agency***

URL: https://www.clinicaltrialsregister.eu/ctr-search/search

Type of search: Basic Search

| Search strategy |
|---|
| (bisphosphonat* OR alendronat* OR "MK 217" OR ibandronat* OR risedron* OR "NE 58095" OR zoledron* OR "ZOL 446" OR "CGP-42446" OR teriparatid* OR LY333334 OR PF708 OR denosumab* OR "AMG 162") AND (osteoporo* OR osteopen*) |

**3. International Clinical Trials Registry Platform Search Portal**

***Provider: World Health Organization***

URL: http://apps.who.int/trialsearch

Type of search: Standard Search

| Search strategy |
|---|
| bisphosphonate AND osteoporosis OR alendronate AND osteoporosis OR MK 217 AND osteoporosis OR ibandronate AND osteoporosis OR risedron* AND osteoporosis OR NE 58095 AND osteoporosis OR zoledron* AND osteoporosis OR ZOL 446 AND osteoporosis OR CGP-42446 AND osteoporosis OR teriparatide AND osteoporosis OR LY333334 AND osteoporosis OR PF708 AND osteoporosis OR denosumab AND osteoporosis OR AMG 162 AND osteoporosis OR bisphosphonate AND osteopenia OR alendronate AND osteopenia OR MK 217 AND osteopenia OR ibandronate AND osteopenia OR risedron* AND osteopenia OR NE 58095 AND osteopenia OR zoledron* AND osteopenia OR ZOL 446 AND osteopenia OR CGP-42446 AND osteopenia OR teriparatide AND osteopenia OR LY333334 AND osteopenia OR PF708 AND osteopenia OR denosumab AND osteopenia OR AMG 162 AND osteopenia |

## A.3 Further information sources and search techniques

**Regulatory authorities**

***EMA***

URL: https://www.ema.europa.eu/en/medicines

| Search terms |
|---|
| Fosamax, Adrovance, Fosavance, Binosto, Vantavo, Bonviva, Bondenza, Actonel, Aclasta, Forsteo, Terrosa, Movymia, Prolia |

***FDA***

URL: https://www.accessdata.fda.gov/scripts/cder/daf/

| Search terms |
|---|
| Fosamax, Binosto, Fosamax plus D, Boniva, Actonel, Actonel with Calcium, Atelvia, Reclast, Forteo, Prolia |

**G-BA-Website und IQWiG-Website**

***G-BA***

URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/

| Search terms |
|---|
| osteoporose |

***IQWiG***

URL: https://www.iqwig.de/

| Search terms |
|---|
| osteoporose |