Common Drug Review
Clinical Review Report

October 2015

Drug	denosumab (Prolia)
Indication	Treatment to increase bone mass in men with osteoporosis at high risk for fracture; or who have failed or are intolerant to other available osteoporosis therapy
Listing request	As per indication
Dosage form(s)	60 mg/mL solution for injection
NOC date	November 21, 2012
Manufacturer	Amgen Canada

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in rheumatology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from CDR Clinical and Pharmacoeconomic Review Reports.

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TABLE OF CONTENTS

Tables

Figure

ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BMD	bone mineral density
CI	confidence interval
CDR	CADTH Common Drug Review
CRF	clinical risk factor
DB	double-blind
GR	gradient of risk
IDC	indirect comparison
ITT	intention-to-treat population
LOCF	last observation carried forward
MCID	minimal clinically important difference
PP	per protocol
Q6M	single doses at the first and sixth months
RANKL	human receptor activator of nuclear factor kappa-B ligand
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing patients to an increased risk of fracture.[1] In men, coexisting conditions and risk factors often combine with age-related, slowly proceeding bone loss to result in osteoporosis and fragility fractures.[2] Osteoporotic fractures are a significant health care concern with devastating impacts on patients, often leading to an increased risk of subsequent fracture, hospitalization, decreased quality of life, premature mortality, and increased burden on the health care system.[3] For men requiring treatment of osteoporosis, the Osteoporosis Canada 2010 guidelines recommend the oral bisphosphonates alendronate and risedronate, as well as the parenteral bisphosphonate zoledronic acid, as first-line treatment options.[4]

Denosumab is a human monoclonal antibody binding to human receptor activator of nuclear factor kappa-B ligand (RANKL).[5] Denosumab has a Health Canada indication as treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or in patients who have failed or are intolerant to other available osteoporosis therapy.[5] The drug plans that participate in the CADTH Common Drug Review (CDR) process have requested that denosumab be evaluated for reimbursement for treating osteoporosis in men according to the Health Canada indication. The objective of this report was to perform a systematic review of the beneficial and harmful effects of denosumab as a treatment to increase bone mass in men with osteoporosis at high risk for fracture, or who have failed or are intolerant to other available osteoporosis therapy.

Results and Interpretation

Included Studies

One published, manufacturer-sponsored, double-blind (DB), randomized controlled trial (RCT) was included in the systematic review. ADAMO (n = 242)[6,7] evaluated the superiority of denosumab compared with placebo by assessing changes in lumbar spine bone mineral density (BMD) after 12 months of treatment in men with low BMD, defined in the trial as a T-score ≤ –2 or a T-score ≤ –1 in patients with a history of major osteoporotic fracture. Patients randomized to denosumab received a dose of 60 mg by subcutaneous (SC) injection every six months. All patients received concomitant treatment with calcium and vitamin D. The primary efficacy outcome for ADAMO was the mean per cent change in lumbar spine BMD after 12 months of treatment.

ADAMO was conducted with methodological rigour. One limitation of the study was the fact that treatment response was assessed using change in BMD rather than the incidence of fractures, which is the most important outcome for patients according to the patient input received by CADTH; consequently, there is no direct evidence regarding the effects of denosumab on reducing the incidence of fractures in men. However, BMD is widely accepted as a suitable outcome for clinical trials of osteoporosis treatments, and the fact that denosumab has been shown to reduce the incidence of new vertebral and hip fractures in women with post-menopausal osteoporosis suggests that similar clinical benefits could occur also in men. Another limitation of the study is that the trial population comprised patients who were at a lower risk of sustaining a fracture than the population likely to be seen in clinical practice in Canada, according to the clinical expert consulted by CDR reviewers. Although the trial population in ADAMO was at increased risk of fracture, patients who were at the highest risk of fracture based on their BMD values or fracture history were excluded from the trial, and the proportion of patients who sustained a prior fracture was lower than would be expected in clinical practice. In

addition, patients with various comorbid conditions commonly seen in clinical practice were excluded from the study, including those with impaired renal function, [redacted]. The exclusion of patients who received bisphosphonate treatment within the last two years is also not representative of current practice, as bisphosphonates remain the first-line treatment option for men with low BMD. This is potentially important when interpreting the relative efficacy of denosumab compared with other drugs, because it is possible that patients treated recently with bisphosphonates who are switched to denosumab treatment could experience a smaller improvement in BMD compared with previously untreated patients.

Efficacy

Results from the ADAMO study demonstrate the superiority of denosumab over placebo, based on the primary outcome of change in lumbar spine BMD after 12 months. The difference between treatment groups was statistically significant and reached 4.8% (95% confidence interval [CI], 4.0 to 5.6; $P < 0.0001$). The use of denosumab was associated with a mean per cent change from baseline of 5.7% (95% CI, [redacted]), which was considered clinically significant, as experience from the clinical expert consulted by CDR suggests a minimal clinically important difference (MCID) of 3% for lumbar spine BMD. The small improvement of 0.9% (95% CI, [redacted]) in the placebo group likely resulted from the concomitant administration of calcium and vitamin D.

The manufacturer elected to use measures at the lumbar spine for the primary outcome, because this site is more metabolically active and more responsive to treatment.[8] However, the effects of denosumab were also superior to placebo for the secondary outcomes of change from baseline in total hip and lumbar spine BMD, although the magnitude of the between-group difference at these other anatomical sites was smaller, as they show a slower response to treatment. The ADAMO study did not provide evidence to inform on the effects of denosumab on clinical outcomes such as fractures and quality of life, which were identified as the most important outcomes according to patient input. Although widely used in clinical practice, change in BMD is a surrogate outcome that does not consider other independent clinical risk factors for fractures. Unfortunately, fractures were not assessed as an efficacy outcome in ADAMO. The Canadian Expert Drug Advisory Committee (CEDAC) recommended in 2011 that denosumab be reimbursed for women with post-menopausal osteoporosis, based on a statistically significantly greater reduction in the incidence of new vertebral and hip fractures achieved by denosumab compared with placebo. It is uncertain whether the clinical benefits of denosumab on BMD observed in men in ADAMO would translate to a corresponding reduction in fracture risk as in post-menopausal women, although it is likely, given that the BMD increase in response to denosumab observed in men in ADAMO was similar to that observed in post-menopausal women with osteoporosis after 12 months of treatment in three other clinical studies (5% to 6%).

Long-term maintenance of denosumab effectiveness was documented during the ADAMO subsequent 12-month open-label phase, during which all patients received denosumab. Lumbar spine BMD continued to increase in patients already receiving denosumab, with a per cent change from baseline reaching 8.0% (95% CI, [redacted]) after 24 months. Patients transitioning from placebo to denosumab had BMD increases similar in magnitude to those of patients receiving denosumab in the DB phase (5.7%; 95% CI, [redacted]).

There is a lack of evidence with which to directly compare denosumab with other drugs used for the treatment of osteoporosis in men. To fill this evidence gap, a literature review was conducted by CDR. No published indirect comparisons (IDCs) were retrieved in the literature, but the review team conducted a critical appraisal of two IDCs provided by the manufacturer, in which the efficacy of

denosumab was compared with zoledronic acid in men with osteoporosis.[9] The first IDC compared denosumab with zoledronic acid in a two-step loop. The first step compared denosumab with alendronate through placebo as the common comparator, and the second step was through the direct comparison between alendronate and zoledronic acid. The second IDC compared denosumab with zoledronic acid in a one-step loop that had placebo as the only common comparator. The results of the two IDCs were consistent in demonstrating that there are no statistically significant differences between the effects of denosumab and zoledronic acid on the change in BMD after 12 months in the hip, femoral neck, and trochanter. In one of the two IDCs, denosumab was associated with a small but statistically significantly greater improvement in BMD versus zoledronic acid in only the lumbar spine, but no such difference was detected in the other IDC. The small number of studies available and the correspondingly small number of included patients mean that the effects of heterogeneity among studies on the comparative efficacy of the treatments are highly uncertain. Therefore, the overall results of the IDCs are consistent with the conclusion that there is no clear evidence of clinically relevant differences with respect to the increase in BMD associated with denosumab and zoledronic acid treatment in men with osteoporosis.

Harms

Denosumab is approved for six indications and has been in use since 2010, and the overall harms in ADAMO results did not raise any new safety concerns. Additional safety data included the ADAMO open-label phase and showed that the overall frequency and type of adverse events (AEs) observed in the DB phase did not change over the long term in patients who continued denosumab through 24 months, as well as in patients who transitioned from placebo to denosumab for a 12-month open-label treatment period.

Mortality as well as the overall incidence of serious adverse events (SAEs) during ADAMO did not differ significantly between denosumab and placebo, and were not higher than would be expected in this patient population in clinical practice, according to the clinical expert consulted by CDR. The most commonly reported SAEs for both treatments were infrequent (< 2.5%) and included prostate cancer, arterial thrombosis, pancreatitis, peripheral ischemia, myocardial infarction, and chest pain. The proportion of patients experiencing AEs was also similar between denosumab and placebo. The most common AEs included back pain, arthralgia, and nasopharyngitis. Limited proportions of patients discontinued due to AEs in the denosumab treatment group, suggesting adequate tolerability.

Some AEs of particular interest were identified by CDR based on the denosumab mechanism of action and Health Canada warnings, which have been issued with regard to the risks of hypocalcemia, infections, dermatologic AEs, osteonecrosis of the jaw, atypical femur fractures, and malignancies.[5] There were no reports of osteonecrosis of the jaw, atypical femur fractures, fracture healing complications, or hypocalcemia throughout the ADAMO study duration. Results for other notable AEs are characterized by a low number of events reported in both treatment groups. The only exception pertains to infections, which were experienced by 20% of patients in both treatment groups.

There were no reports of gastrointestinal disorders with denosumab throughout the ADAMO trial. The patient input received by CDR indicated that patients who do not tolerate oral bisphosphonates due to gastrointestinal disorders or problems swallowing expect to see fewer AEs with denosumab injections, thereby increasing the probability of treatment adherence and effectiveness.

No data are available to directly compare the potential harms of denosumab versus other active treatment options for men with osteoporosis. The potential harms were not analyzed in the two available IDCs to compare the safety of denosumab with zoledronic acid. However, the available evidence (i.e., the proportions of patients experiencing AEs and SAEs in the included studies used in the IDCs) suggests that denosumab and zoledronic acid likely do not have markedly different safety profiles. Nevertheless, given the aforementioned limitations of the indirect comparisons (most notably the small number of studies and included patients), there is a high degree of uncertainty related to interpreting the comparative safety profile associated with denosumab compared with zoledronic acid.

Conclusions

The results of the ADAMO study demonstrated the superiority of denosumab over placebo for improving lumbar spine BMD after 12 months of treatment in men with low BMD. In the open-label extension phase, denosumab continued to be effective in improving BMD up to 24 months. However, the trial did not provide evidence to inform on the effects of denosumab on clinical outcomes such as fractures and quality of life. There were no reports of osteonecrosis of the jaw, atypical femur fractures, fracture healing complications, or hypocalcemia. Few patients experienced dermatologic AEs or malignancies, and similar proportions of patients developed infections in both treatment groups. The generalizability of the results of ADAMO is limited by the fact that the trial population had a slightly lower risk of fracture than that seen in clinical practice, as well as by the exclusion of patients with commonly seen comorbid conditions, and by the exclusion of patients who had received recent bisphosphonate treatment. The results of two indirect comparisons submitted by the manufacturer in which the efficacy of denosumab was compared with zoledronic acid were consistent with the conclusion that denosumab is at least as effective as zoledronic acid for increasing BMD in men with osteoporosis.

TABLE 1: SUMMARY OF RESULTS

	ADAMO	
	Denosumab	Placebo
Key Efficacy Outcomes	**N = 117**	**N = 118**
Vertebral, Hip, and Other Non-Vertebral Fractures		
No data reported		
Per Cent Change from Baseline in BMD		
Lumbar Spine BMD		
Per Cent Change from Baseline at Month 12 (Primary Outcome in the Trial)		
LS mean (95% CI)	5.7 (5.1 to 6.2)	0.9 (0.3 to 1.4)
Difference from Placebo — Primary Efficacy Population, LOCF		
LS mean (95% CI), *P* value	4.8 (4.0 to 5.6), *P* < 0.0001	
Total Hip BMD — Difference from Placebo at Month 12		
Estimate (95% CI), *P* value	2.0 (1.5 to 2.6), *P* < 0.0001	
Femoral Neck BMD — Difference from Placebo at Month 12		
Estimate (95% CI), *P* value	2.2 (1.3 to 3.0), *P* < 0.0001	
Health-Related Quality of Life		
No data reported		
Hospitalizations		
No data reported		
Key Harms Outcomes	**N = 120**	**N = 120**
Mortality, n (%)	1 (0.8)	1 (0.8)
SAEs, n (%)	11 (9.2)	10 (8.3)
AEs, n (%)	86 (71.7)	84 (70.0)
WDAEs, n (%)	3 (2.5)	0
Notable Harms	**N = 120**	**N = 120**
Atypical femur fractures	0	0
Cardiac disorders AEs	[redacted]	3 (2.5)
Cardiac disorders SAEs	2 (1.7)	1 (0.8)
Eczema	2 (1.7)	0
Fracture healing complications	0	0
Hypocalcemia	0	0
Infection — AEs	24 (20.0)	24 (20.0)
Infection — SAEs	0	1 (0.8)
Malignancy	4 (3.3)	0
Osteonecrosis of the jaw	0	0
Skin infection — AEs	0	1 (0.8)

AE = adverse event; BMD = bone mineral density; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Note: The primary outcome in the ADAMO study was the mean per cent change in lumbar spine BMD at 12 months.

[redacted]

Source: Clinical Study Report.[8]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing patients to an increased risk of fracture.[1] Unlike in women, who experience a loss of hormone production during menopause leading to accelerated bone changes, the bone loss that occurs in men proceeds slowly.[2] In men, coexisting conditions and risk factors often combine with age-related bone loss to result in osteoporosis and fragility fractures.[2] Young men may also experience idiopathic osteoporosis, for which the pathogenesis is uncertain.[2]

Possible consequences of fracture include an increased risk of subsequent fracture, hospitalization and institutionalization, decreased quality of life, premature mortality, and increased burden on the health care system.[3] According to the patient input received by CDR, the effects of fractures on patients can be devastating and include loss of independence, decreased mobility, isolation, and depression. Well-established risk factors for osteoporotic fractures include older age, low bone mineral density (BMD), and history of fracture.[4] Other risk factors include parental history of hip fracture, current tobacco smoking, long-term use of oral glucocorticoids, and high alcohol consumption.[10]

Statistics from Osteoporosis Canada suggests that at least one in five men will experience a fracture from osteoporosis during their lifetime. In Canada, about 7,500 men sustain hip fractures yearly and are more likely to die of complications from a hip fracture than women. The care gap for men is greater than for women. In general, fewer than 20% of fracture patients receive assessment and treatment for underlying osteoporosis; for men, that percentage is less than 10%.

1.2 Standards of Therapy

The Osteoporosis Canada 2010 guidelines signified a paradigm shift in the prevention and treatment of osteoporotic fractures, moving the focus from treating low BMD to better identifying the risk of fragility fractures in patients.[4] Two tools are available in Canada for estimating the 10-year risk of a major osteoporotic fracture:[4]

- the updated tool of the Canadian Association of Radiologists and Osteoporosis Canada (CAROC)
- the Fracture Risk Assessment tool (FRAX) of the World Health Organization (WHO).

Both tools incorporate age, sex, prior fragility fracture, and systemic corticosteroid use, together with BMD to define the fracture risk.[4] Based on these tools, patients with a moderate 10-year fracture risk (10% to 20%) or a high fracture risk (> 20% or prior fragility fracture) will benefit from pharmacological treatment.[4] For men requiring treatment of osteoporosis, the oral bisphosphonates alendronate and risedronate, as well as the parenteral bisphosphonate zoledronic acid, are considered first-line treatment options for prevention of fractures.[4] However, for patients who receive an intervention, only a minority will adhere for any meaningful duration.[11]

1.3 Drug

Denosumab is a human monoclonal antibody binding with affinity and specificity to human receptor activator of nuclear factor kappa-B ligand (RANKL).[5] By neutralizing the activity of RANKL, denosumab decreases osteoclast-mediated bone resorption through inhibition of osteoclast formation, function, and survival.[5] Denosumab has a Health Canada indication as treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or in patients who have failed or are intolerant to other available osteoporosis

therapy.[5] The recommended dose of denosumab is a 60 mg subcutaneous (SC) injection every six months.[5]

Indication under review
Treatment to increase bone mass in men with osteoporosis at high risk for fracture; or who have failed or are intolerant to other available osteoporosis therapy
Listing criteria requested by participating drug plans
Treatment to increase bone mass in men with osteoporosis at high risk for fracture; or who have failed or are intolerant to other available osteoporosis therapy

Denosumab is indicated in post-menopausal women with osteoporosis at high risk for fracture.[5] The Canadian Expert Drug Advisory Committee (CEDAC) recommended in its 2011 Final Recommendation that denosumab be listed for women with post-menopausal osteoporosis who would otherwise be eligible for jurisdictional funding for oral bisphosphonates, but for whom bisphosphonates are contraindicated due to hypersensitivity or abnormalities of the esophagus (e.g., esophageal stricture or achalasia), and who have at least two of the following:

- age > 75 years
- a prior fragility fracture
- a BMD T-score ≤ –2.5.

Denosumab (Prolia) is also indicated as treatment to increase bone mass in men with non-metastatic prostate cancer receiving androgen deprivation therapy who are at high risk for fracture, as well as in women receiving adjuvant aromatase inhibitor therapy for non-metastatic breast cancer.[5] Finally, denosumab is available in a different product formulation (Xgeva) that is indicated in some cases of metastatic tumour and giant cell tumour of bone.[5]

TABLE 2: KEY CHARACTERISTICS OF DENOSUMAB AND BISPHOSPHONATES INDICATED IN MEN WITH OSTEOPOROSIS

	Denosumab[5]	Bisphosphonates Alendronate, Risedronate, and Zoledronic Acid (Aclasta)[12-15]
Mechanism of Action	Human monoclonal antibody that inhibits osteoclast-mediated bone resorption	Synthetic analogues of pyrophosphate that bind to the hydroxyapatite found in bones and inhibit osteoclast-mediated bone resorption
Indication[a]	Treatment to increase bone mass in men with osteoporosis at high risk for fracture	• Alendronate: treatment of osteoporosis in men to reduce the incidence of fractures • Risedronate: treatment of osteoporosis in men to improve bone mineral density • Zoledronic acid: treatment to increase bone mineral density in men with osteoporosis
Route of Administration	SC injection	• Alendronate: oral • Risedronate: oral • Zoledronic acid: IV infusion
Recommended Dose	60 mg SC every six months	• Alendronate: 70 mg PO weekly or 10 mg PO daily • Risedronate: 35 mg PO weekly • Zoledronic acid: once-yearly single IV infusion
Common Serious Side Effects and Safety Issues	Osteonecrosis of the jaw, atypical femoral fractures, hypocalcemia	
Particular Serious Side Effects and Safety Issues	Infections, dermatologic AEs	Deterioration in renal function, musculoskeletal pain, cardiovascular and gastrointestinal AEs

AE = adverse event; IV = intravenous; PO = orally; SC = subcutaneous.
[a] Relevant Health Canada indications.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of denosumab as a treatment to increase bone mass in men with osteoporosis at high risk for fracture, or who have failed or are intolerant to other available osteoporosis therapy.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Men with osteoporosis who are at high risk for fracture, or who have failed or are intolerant to other available osteoporosis therapy
Intervention	Denosumab 60 mg SC every six months
Comparators	Alendronate 70 mg PO once weekly or 10 mg PO q.d. Risedronate 35 mg PO once weekly Zoledronic acid (Aclasta only) once-yearly single IV infusion Placebo
Outcomes	**Key efficacy outcomes:** Vertebral, hip, and other non-vertebral fractures Change in BMD Health-related quality of life Hospitalizations **Harms outcomes:** Mortality SAEs WDAEs AEs including but not limited to: • Osteonecrosis of the jaw • Atypical femoral fractures • Infections • Hypocalcemia • Dermatologic adverse events
Study Design	Published RCTs

AE = adverse event; BMD = bone mineral density; IV = intravenous; PO = orally; q.d. = once daily; RCT = randomized controlled trial; SC = subcutaneous; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Note: All medications should be given concomitantly with calcium and vitamin D supplementation.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Prolia (denosumab) and men.

Methodological filters were applied to limit retrieval to randomized controlled trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on February 11, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on August 19, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), Internet Search. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of 272 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

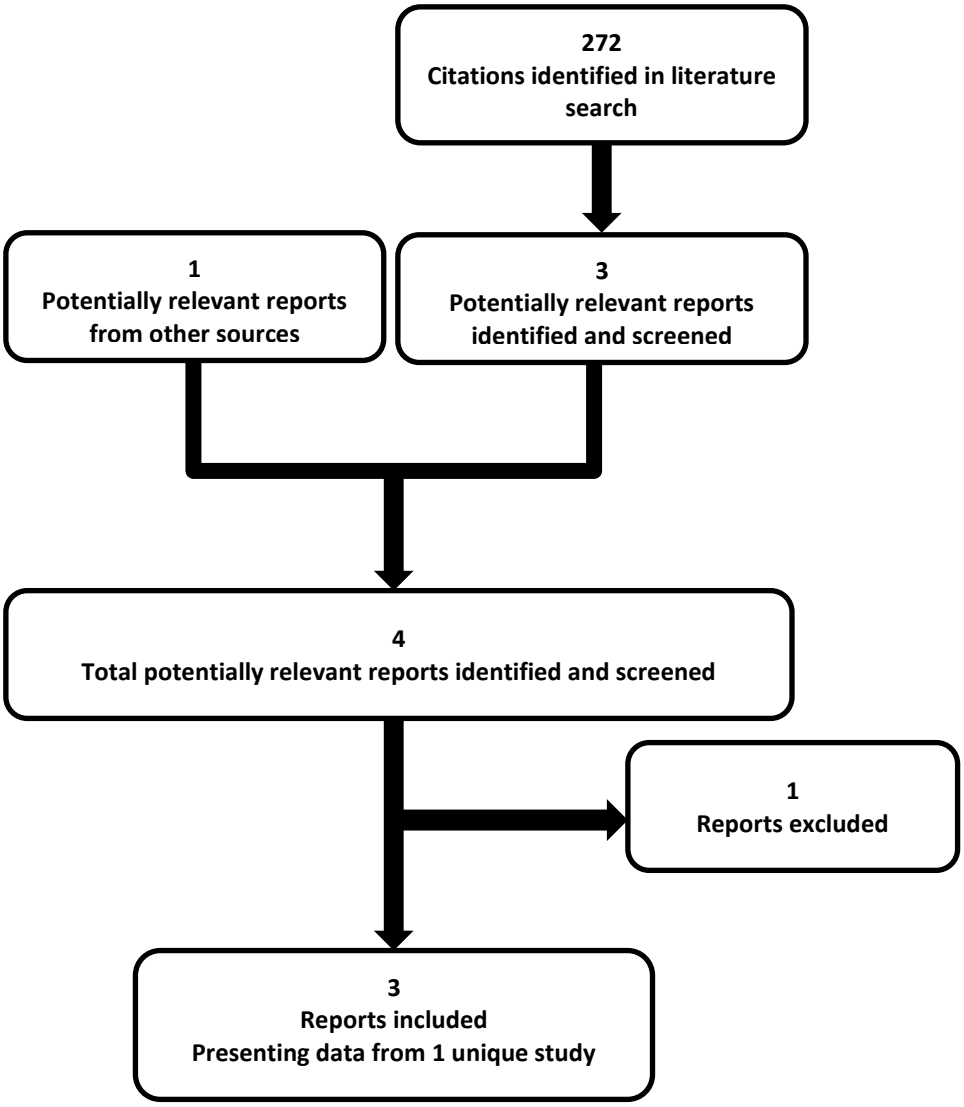


TABLE 4: DETAILS OF INCLUDED STUDIES

		ADAMO
DESIGNS & POPULATIONS	**Study Design**	DB placebo-controlled RCT with O/L extension phase
	Locations	Multi-centre (27 study centres): Europe, US, Canada
	Randomized (N)	242
	Inclusion Criteria	Men between 30 and 85 years with low BMD, defined as: • T-score ≤ –2; or • T-score ≤ –1 in patients with a history of major osteoporotic fracture.
	Exclusion Criteria	Severe to moderate vertebral fracture at screening; vertebral or clinical fracture within six months; T-score < –3.5; concomitant metabolic bone disease or malabsorption syndrome; prior use of denosumab; bisphosphonates within two years; vitamin D deficiency; abnormal thyroid or parathyroid function; elevated transaminase; significantly impaired renal function; hypo- or hypercalcemia; bilateral hip replacement; known HIV, hepatitis B or C; liver cirrhosis; malignancy within five years; transplant or chronic immunosuppression.
DRUGS	**Intervention**	Denosumab 60 mg SC every six months; given concomitantly with daily calcium (≥ 1,000 mg of elemental calcium) and vitamin D (≥ 800 IU) supplementation.
	Comparator(s)	Placebo; given concomitantly with daily calcium (≥ 1,000 mg of elemental calcium) and vitamin D (≥ 800 IU) supplementation.
DURATION	**Phase**	
	Double-blind	12 months
	Open-label extension	12 months All patients received denosumab up to a total of 24 months, independent of randomization
OUTCOMES	**Primary End Point**	Mean per cent change in lumbar spine BMD at 12 months
	Other End Points	Mean per cent change in BMD at 12 months at the following sites: • total hip; and • femoral neck.
NOTES	**Publications**	Orwoll et al. 2012; Langdahl et al. 2015[6,7]

BMD = bone mineral density; DB = double-blind; IU = international units; O/L = open-label; RCT = randomized controlled trial; SC = subcutaneous.
Note: One additional report was included.[8]
Source: Orwoll et al. 2012; Langdahl et al. 2015; Clinical Study Report.[6-8]

3.2 Included Studies

3.2.1 Description of studies

One published, manufacturer-sponsored, double-blind (DB), randomized controlled trial (RCT) was included in the systematic review. ADAMO (n = 242)[6,7] evaluated the superiority of denosumab compared with placebo based on lumbar spine BMD after 12 months of treatment in men with low BMD, which was defined in the trial as:

- T-score ≤ –2; or
- T-score ≤ –1 in patients with a history of major osteoporotic fracture.

Patients randomized to denosumab received a dose of 60 mg administered by subcutaneous (SC) injection every six months; all patients received concomitant treatment with calcium (1,000 mg of elemental calcium) and vitamin D (800 IU). The trial was designed with a subsequent 12-month open-label phase during which all patients received denosumab, regardless of randomization (discussed in APPENDIX 6: SUMMARY OF A LONG-TERM EXTENSION STUDY).

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients were eligible for the ADAMO study if they were ambulatory men between 30 and 85 years of age at the start of screening. The trial used the following inclusion criterion of BMD:

- T-score ≤ –2 at the lumbar spine or femoral neck; or
- T-score ≤ –1 at the lumbar spine or femoral neck in patients with a history of major osteoporotic fracture (e.g., clinical vertebral, hip, humerus, and distal radius fractures) occurring more than six months prior to screening.

Key exclusion criteria included patients with any severe or moderate vertebral fractures at screening, any vertebral fracture or clinical fracture that occurred within the previous six months, as well as patients with BMD values at screening that were considered too low (T-score < –3.5). Patients were also excluded if they had any metabolic bone disease or evidence of malabsorption syndrome that had the potential to interfere with the interpretation of the findings. The presence of the following comorbidities also excluded patients from participating in the trial: vitamin D deficiency (< 49.9 nmol/L or 20 ng/mL); abnormal thyroid or parathyroid function; elevated transaminase; significantly impaired renal function; hypo- or hypercalcemia; bilateral hip replacement; known HIV, hepatitis B or C, or liver cirrhosis; malignancy at screening or within the prior five years; as well as any transplant or chronic immunosuppression.

Prior use of denosumab and administration of oral or intravenous (IV) bisphosphonates within the past two years also figured as exclusion criteria. The following therapies were prohibited as well within three months of screening: anabolic steroids or testosterone; glucocorticoids; calcitonin, calcitriol or vitamin D derivatives (supplements and multivitamins permitted); other bone active drugs; chronic systemic ketoconazole, adrenocorticotrophic hormone, cinacalcet, aluminum, lithium, protease inhibitors, methotrexate, and gonadotropin-releasing hormone agonists; as well as androgen deprivation therapy.

b) Baseline characteristics

Details regarding baseline characteristics are provided in Table 5. Patients in the ADAMO trial had a mean age of 65 years, with close to 90% of the population ranging from 50 to 79 years. All patients were men and 94% were Caucasian. Approximately half of patients had a T-score ≤ –2.5; the mean baseline T-score at lumbar spine was –2.0. The mean 10-year major osteoporotic fracture risk was 10% ± 6%.

Baseline characteristics were balanced between treatment groups, with the exception of history of fractures. Close to 40% of patients in the ADAMO trial sustained a previous fracture; however, 19% of patients in the denosumab group experienced an osteoporotic fracture, compared with 31% of patients in the placebo group. Major osteoporotic fractures were experienced by 13% of patients randomized to denosumab and 17% of patients randomized to placebo. Prevalent vertebral fractures were more frequent in the denosumab group compared with placebo (25% versus 21%, respectively).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

	ADAMO	
	Denosumab N = 121	Placebo N = 121
Age		
Mean ± SD, years	64.9 ± 10.5	65.0 ± 9.1
< 50 years, n (%)	9 (7.4)	5 (4.1)
50 to 59 years, n (%)	22 (18.2)	26 (21.5)
60 to 69 years, n (%)	44 (36.4)	49 (40.5)
70 to 79 years, n (%)	39 (32.2)	35 (28.9)
≥ 80 years, n (%)	7 (5.8)	6 (5.0)
Gender, n (%)		
Male	121 (100.0)	121 (100.0)
Ethnic Group, n (%)		
Caucasian	121 (100.0)	107 (88.4)
Other	0	14 (11.6)
Minimum T-Score at Lumbar Spine or Femoral Neck, n (%)		
≤ –2.5	61 (50.4)	56 (46.3)
> –2.5	60 (49.6)	65 (53.7)
T-Score — Lumbar Spine		
Mean ± SD (range)	–2.0 ± 1.1 (–3.6 to 2.1)	–2.0 ± 1.0 (–3.6 to 2.3)
T-Score — Total Hip		
Mean ± SD (range)	–1.5 ± 0.6 (–3.5 to 0.2)	–1.4 ± 0.7 (–2.8 to 0.1)
T-Score — Femoral Neck		
Mean ± SD (range)	–1.9 ± 0.6 (–3.8 to 0.7)	–1.9 ± 0.6 (–3.4 to 0.3)
History of Fracture, n (%)		
Any fracture	47 (38.8)	48 (39.7)
Osteoporotic[a]	23 (19.0)	37 (30.6)
Major osteoporotic[b]	16 (13.2)	20 (16.5)
Prevalent vertebral fracture	30 (24.8)	25 (20.7)
10-year major osteoporotic fracture risk with BMD, %		
Mean ± SD	9.87 ± 6.28	9.72 ± 6.40
Range	(1.6 to 38.7)	(1.6 to 42.3)
Total Testosterone		
Mean ± SD, ng/dl	368.4 ± 121.0	356.4 ± 116.7

BMD = bone mineral density; SD = standard deviation.
[a] Osteoporotic fractures were defined as vertebral or non-vertebral fractures with low trauma.[6]
[b] Major osteoporotic fractures were defined as hip, spine, forearm, or humerus fractures with low trauma.[6]
Sources: Orwoll et al. 2012; Clinical Study Report.[6,8]

3.2.3 Interventions

ADAMO evaluated the efficacy and safety of denosumab for the treatment of men with low BMD, at the recommended dose of 60 mg administered subcutaneously every six months. This placebo-controlled study was conducted in a double-blind fashion; therefore, patients randomized to the control group received matching placebo. All patients also received concomitant treatment with calcium (1,000 mg of elemental calcium) and vitamin D (800 IU). However, the concomitant use of any other medication known to have a suspected activity on bone metabolism was not permitted.

3.2.4 Outcomes

The primary efficacy outcome for ADAMO was the mean per cent change in lumbar spine BMD after 12 months of treatment. BMD was assessed by dual-energy X-ray absorptiometry (DXA) scans submitted electronically for final blinded analysis. Secondary efficacy outcomes were the mean per cent change in BMD after 12 months at total hip and femoral neck. Harms outcomes included adverse events (AEs), serious adverse events (SAEs), clinical laboratory results, and vital signs.

3.2.5 Statistical analysis

The primary objective of ADAMO was to test for superiority of denosumab compared with placebo in men with low BMD for the outcome of lumbar spine BMD after 12 months of treatment, based on the mean per cent change. The analysis of the per cent change from baseline in lumbar spine BMD to month 12 was performed using an analysis of covariance (ANCOVA) model with last observation carried forward (LOCF) imputation. The ANCOVA model included treatment as the main effect and the level of baseline BMD T-score (randomization stratification factor) as the covariate. The primary results were based on the point estimate for the least squares means and the two-sided 95% confidence interval (CI) for the treatment difference (denosumab — placebo) at the 12-month time point.[8]

The sample size was computed based on the secondary outcome with the least power. For the primary outcome, inclusion of 242 patients in the ADAMO study provided a minimum of 99% power to detect a 5.1% difference at lumbar spine between the treatment groups at month 12, assuming a standard deviation (SD) of 3.8% and a two-sided alpha of 0.05.[8]

a) Analysis populations

The **primary analysis population** included all randomized patients with a non-missing baseline evaluation and at least one post-baseline evaluation at or prior to month 12. Patients were analyzed according to their original randomized treatment assignment, regardless of treatment received. Efficacy analyses also included a **per-protocol population**, which consisted of a subset of patients from the primary analysis who were compliant with the protocol. For patients who received proscribed therapy or a study drug that differed from that assigned at randomization, all data collected after the first occurrence of either event were excluded from this per-protocol analysis.

The **safety analysis population** included all randomized patients who received at least one dose of study drug. For the purpose of safety analyses, patients were categorized according to the actual treatment received; therefore, patients who received at least one dose of denosumab were analyzed in the denosumab treatment group regardless of randomization.

3.3 Patient Disposition

Details regarding baseline characteristics are provided in Table 6. A total of 242 patients were enrolled and randomized in the ADAMO study; of these, 95% completed the 12-month DB phase. Discontinuation rates throughout the study duration, as well as reasons for discontinuation, were slightly higher in the

denosumab group compared with placebo. A total of 7% of patients randomized to denosumab and 3% of patients receiving placebo discontinued from the trial; the most frequent reasons for discontinuation were withdrawal of consent (3% and < 1%, respectively) and adverse events (2% and 0%, respectively).

TABLE 6: PATIENT DISPOSITION

Patient Disposition	ADAMO	
	Denosumab	Placebo
Enrolled, N	242	
Randomized — Overall	242	
Randomized — Per group	121	121
Randomized and Treated, n (%)	120 (99)	120 (99)
Completed Double-Blind Phase (12 months)	111 (92)	117 (97)
Discontinued[a], n (%)	9 (7)	3 (3)
Most Frequent Reasons for Discontinuation, n		
Withdrawal of consent	4 (3)	1 (< 1)
Adverse events	3 (2)	0
Death	1 (< 1)	1 (< 1)
Ineligibility determined	1 (< 1)	1 (< 1)
Completed Open-Label Extension (24 months)	105 (87)	114 (94)
Analysis Sets		
ITT, N	117	[redacted]
PP, N	[redacted]	[redacted]
Safety, N	120	120

ITT = intention-to-treat population; PP = per-protocol set.
[a] Discontinued study treatment and withdrew from the study.
Sources: Orwoll 2012, p. 3163; Langdahl 2015, p. 4; Clinical Study Report, p. 89.[6-8]

3.4 Exposure to Study Treatments

Of the 240 patients randomized in the ADAMO study and treated, [redacted] patients received the two planned injections of study drug given during the 12-month DB period ([redacted] patients in the denosumab group and [redacted] patients in the placebo group). A total of [redacted] patients received only one dose of study drug ([redacted] patients in the denosumab group and [redacted] patients in the placebo group).

3.5 Critical Appraisal

3.5.1 Internal validity

a) Study design, intervention, and comparator

ADAMO was a DB, placebo-controlled, randomized trial that was likely conducted with methodological rigour. However, there is a lack of evidence with which to directly compare denosumab with other drugs recommended for the treatment of osteoporosis in men. To fill this gap, additional evidence was gathered in the form of indirect comparisons.

b) Selection, allocation, and disposition of patients

The ADAMO trial was performed using appropriate allocation strategies. Patients were randomized in a 1:1 allocation to receive denosumab or placebo; the randomization schedule was stratified by BMD

value. The randomization schedule used randomly permuted blocks and was performed centrally through an interactive voice response system. The trial was conducted in a DB fashion and therefore used a matching placebo solution. There was no indication of unplanned sources of unblinding.

Overall, baseline characteristics were balanced between treatment groups, with the exception of history of fractures. Higher proportions of patients in the placebo group sustained a previous osteoporotic fracture, as well as a major osteoporotic fracture. This suggests that patients in the placebo group may have been at higher risk of fracture compared with patients in the denosumab group. However, the impact of this imbalance on the primary efficacy outcome of change in BMD is uncertain.

Discontinuation rates throughout the ADAMO study duration were relatively low, although higher in the denosumab treatment group compared with placebo. This is mainly due to a higher proportion of patients withdrawing consent or discontinuing due to adverse events in the denosumab group. This is not expected to have a major impact on the interpretation of the findings.

c) Outcome measures

The outcome measures and definitions for efficacy outcomes, i.e., change from baseline in BMD, is considered appropriate to evaluate treatment response in clinical practice. Although widely used, BMD is a surrogate outcome and is not entirely representative of the risk of fracture. BMD was assessed using DXA scans that were submitted to the central imaging vendor for final blinded analysis. Experience from the specialist's clinical practice suggests the use of a 3% threshold as a minimal clinically important difference (MCID) for lumbar spine BMD.

d) Statistical analysis

The ADAMO trial had sufficient power to demonstrate statistical significance for testing of the primary hypothesis. The analysis was performed using an ANCOVA model including treatment as the main effect and the level of baseline BMD T-score as the covariate. Missing data were imputed using LOCF — a conservative approach, considering that patients in the active group are expected to improve while patients in the placebo group are expected to be stable.

3.5.2 External validity

a) Patient selection

Inclusion and exclusion criteria appeared relevant and reasonable. However, patients included in the ADAMO study were likely at lower risk of sustaining a fracture than the overall real-life population, according to the clinical expert consulted by CDR. Excluded from the trial were patients with any severe or moderate vertebral fractures at screening, any vertebral fracture or clinical fracture that occurred within the previous six months, as well as patients with BMD values considered too low (T-score < –3.5). In addition, the proportions of patients in the trial who sustained a prior fracture are likely lower than would be expected in a real-life setting.

The exclusion of patients who received bisphosphonate treatment within the last two years is also not representative, as bisphosphonates remain the first-line treatment option for men with low BMD; therefore, real-life patients who would receive denosumab are likely to have received a bisphosphonate within a short period of time. It is expected that patients recently treated with bisphosphonates who would be switched to denosumab may experience a reduced change from baseline in BMD.

The trial population was homogenous, with 94% of patients being Caucasian. Various groups of patients with comorbid conditions commonly seen in clinical practice were excluded as well, including but not

limited to metabolic bone disease or malabsorption syndrome; abnormal thyroid or parathyroid function; significantly impaired renal function; bilateral hip replacement; known HIV, hepatitis B or C; liver cirrhosis; and malignancy within five years. Therefore, the findings from ADAMO are not generalizable to these categories of patients.

b) Treatment regimen and length of follow-up

The ADAMO study used an appropriate and realistic denosumab treatment regimen for men with low BMD. However, there is a gap in the evidence due to the use of placebo as a comparator, as ADAMO does not inform on how denosumab compares with other drugs recommended for the treatment of osteoporosis in men.

The 12-month trial duration was considered appropriate in order to see an adequate response to treatment at the lumbar spine anatomical site. Lumbar spine is a primarily trabecular site and therefore is more metabolically active and more responsive to treatment.[8] The sustainability of beneficial treatment effects and long-term safety beyond 24 months remain uncertain.

c) Outcome measures

Although widely used to monitor response to treatment, change in BMD is a surrogate outcome that does not consider other independent clinical risk factors for fractures. These were not assessed as an efficacy outcome in ADAMO; therefore, there is no evidence to inform on the effects of denosumab on the incidence of fractures, the clinical outcome that is the most important to patients, according to the patient input received by CADTH.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data. No data were reported for health-related quality of life and hospitalizations. Data pertaining to vertebral, hip, and other non-vertebral fractures were reported as adverse events and therefore are discussed under Harms (Section 3.7).

3.6.1 Change in bone mineral density

Results of the ADAMO study for the primary outcome of change in lumbar spine BMD after 12 months of treatment demonstrated that the use of denosumab was associated with a mean per cent change from baseline of 5.7% (95% CI, [redacted]) compared with 0.9% (95% CI, [redacted]) with placebo. Results show that denosumab was superior to placebo, with a statistically significant difference between treatment groups reaching 4.8% (95% CI, 4.0 to 5.6; $P < 0.0001$). The change from baseline in patients treated with denosumab is clinically significant, as experience from the specialist's clinical practice suggests the use of a 3% threshold as an MCID for lumbar spine BMD.

Denosumab also reached superiority over placebo for the secondary outcomes of change from baseline in total hip and lumbar spine BMD. Detailed results are presented in Table 7. The magnitude of the between-group difference is smaller compared with lumbar spine; however, this was considered adequate by the clinical expert consulted by CDR, as these anatomical sites show a slower response to treatment.

TABLE 7: KEY EFFICACY OUTCOMES

	ADAMO	
	Denosumab N = 117	Placebo N = 118
A. Vertebral, Hip, and Other Non-Vertebral Fractures		
No data reported		
B. Per Cent Change from Baseline in BMD		
Lumbar Spine BMD		
Per Cent Change from Baseline at Month 12 (Primary Outcome in the Trial)		
LS mean (95% CI)	5.7 ([redacted])	0.9 ([redacted])
Difference from Placebo — Primary Efficacy Population, LOCF		
LS mean (95% CI), *P* value	4.8 (4.0 to 5.6), $P < 0.0001$	
Total Hip BMD		
Difference from Placebo at Month 12		
Estimate (95% CI), *P* value	2.0 ([redacted]), $P < 0.0001$	
Femoral Neck BMD		
Difference from Placebo at Month 12		
Estimate (95% CI), *P* value	2.2 ([redacted]), $P < 0.0001$	
C. Health-Related Quality of Life		
No data reported		
D. Hospitalizations		
No data reported		

BMD = bone mineral density; CI = confidence interval; LOCF = last observation carried forward; LS = least squares.
Note: The primary outcome in the ADAMO study was the mean per cent change in lumbar spine BMD at 12 months.
Source: Clinical Study Report, pp. 103, 105.[8]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Mortality

A total of one patient in each treatment group died during the ADAMO trial. The causes of death were myocardial infarction (denosumab group) and basilar artery thrombosis (placebo group).

3.7.2 Serious adverse events

Similar proportions of patients experienced SAEs in both treatment groups in ADAMO, with a total of 9% and 8% of patients in the denosumab and placebo groups, respectively. The most common SAEs reported (≤ 2.5% in each treatment group) included prostate cancer, arterial thrombosis limb, pancreatitis, peripheral ischemia, myocardial infarction, and chest pain.

3.7.3 Adverse events

Similar proportions of patients experienced AEs in both treatment groups in ADAMO, with a total of 72% and 70% of patients in the denosumab and placebo groups, respectively. The most common AEs reported (< 8.5% in each treatment group) included back pain, arthralgia, nasopharyngitis, osteoarthritis, myalgia, headache, hypertension, and constipation.

Clinical and vertebral fractures in the ADAMO trial were reported as AEs and were characterized by a low number of events reported in each treatment group for both fracture types. One patient (0.8%) experienced a clinical fracture with denosumab compared with two patients (1.7%) with placebo: one patient in each treatment group sustained a rib fracture, while the other patient receiving placebo experienced a humerus fracture. In addition to clinical fractures, one patient (0.8%) in the placebo group suffered a new vertebral fracture; none were reported in the denosumab group.

3.7.4 Withdrawals due to adverse events

The proportion of patients discontinuing ADAMO due to adverse events was 2.5% in the denosumab group, while no patients discontinued the trial in the placebo group. The most frequent reasons for discontinuation due to AEs with denosumab (< 1% in each treatment group) were prostate cancer, a traffic accident with traumatic injuries, and increased frequency of upper respiratory tract infections.

3.7.5 Notable harms

Several AEs of particular interest were identified by CDR and by the manufacturer based on the denosumab mechanism of action and Health Canada warnings. Results for these notable AEs are characterized by a low number of events reported in both treatment groups.

There were no reports of osteonecrosis of the jaw, atypical femur fractures, fracture healing complications, or hypocalcemia throughout the ADAMO study duration. A total of four patients in the denosumab group reported a malignancy; three of them were prostate cancer. There were proportionately more cardiac disorders in the denosumab group compared with placebo ([redacted] versus 3%, respectively). A total of 20% of patients in each treatment group experienced an AE of infection, with only one case of serious infection, which occurred in a patient receiving placebo. Two patients suffered from eczema in the denosumab group, while there were no such reports in the placebo group.

TABLE 8: HARMS

Number of Patients with Harms Outcome	ADAMO	
	Denosumab N = 120	Placebo N = 120
Mortality, n (%)	**1 (0.8)**	**1 (0.8)**
Most common reason:		
MI	1 (0.8)	0
Basilar artery thrombosis	0	1 (0.8)
SAEs, n (%)	**11 (9.2)**	**10 (8.3)**
Most common SAEs:		
Prostate cancer	3 (2.5)	0
Arterial thrombosis limb	2 (1.7)	0
Pancreatitis acute	1 (0.8)	1 (0.8)
Peripheral ischemia	1 (0.8)	1 (0.8)
Acute MI	1 (0.8)	0
Chest pain	1 (0.8)	0
MI	1 (0.8)	0
AEs, n (%)	**86 (71.7)**	**84 (70.0)**
Most common AEs:		
Back pain	10 (8.3)	8 (6.7)
Arthralgia	8 (6.7)	7 (5.8)
Nasopharyngitis	8 (6.7)	7 (5.8)
Osteoarthritis	4 (3.3)	2 (1.7)
Myalgia	2 (1.7)	5 (4.2)
Headache	1 (0.8)	5 (4.2)
Hypertension	1 (0.8)	5 (4.2)
Constipation	0	7 (5.8)
WDAEs, n (%)	**3 (2.5)**	**0**
Most common WDAEs:		
Prostate cancer	1 (0.8)	0
Traffic accident and resultant traumatic injuries	1 (0.8)	0
Increased frequency of upper respiratory tract infections	1 (0.8)	0
Notable Harms		
Atypical femur fractures	0	0
Cardiac disorders		
AEs	[redacted]	3 (2.5)
SAEs	2 (1.7)	1 (0.8)
Eczema	2 (1.7)	0
Fracture healing complications	0	0
Hypocalcemia	0	0
Infection		
AEs	24 (20.0)	24 (20.0)
SAEs	0	1 (0.8)

Number of Patients with Harms Outcome	ADAMO	
	Denosumab N = 120	Placebo N = 120
Malignancy	4 (3.3)	0
Osteonecrosis of the jaw	0	0
Skin infection		
AEs	0	1 (0.8)
SAEs	0	0

AE = adverse event; MI = myocardial infarction; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[redacted]

Source: Clinical Study Report, pp. 118-9, 121-5, 127.[8]

4. DISCUSSION

4.1 Summary of Available Evidence

One published, manufacturer-sponsored, DB RCT was included in the systematic review. ADAMO (n = 242)[6,7] evaluated the superiority of denosumab compared with placebo by assessing changes in lumbar spine BMD after 12 months of treatment in men with low BMD, which was defined in the trial as a T-score ≤ –2, or a T-score ≤ –1 in patients with a history of major osteoporotic fracture. Patients randomized to denosumab received a dose of 60 mg SC every six months. All patients received concomitant treatment with calcium and vitamin D. The trial was designed with a subsequent 12-month open-label phase during which all patients received denosumab; this is discussed in APPENDIX 6: SUMMARY OF A LONG-TERM EXTENSION STUDY.

ADAMO was conducted with methodological rigour, but was not without limitations. One limitation of the study was the fact that treatment response was assessed using change in BMD rather than the incidence of fractures. A reduction in the incidence of fractures is the most important outcome for patients, according to the patient input received by CDR, and as BMD change was the primary outcome in ADAMO, there is no direct evidence available to evaluate the effects of denosumab on the incidence of fractures in men. Nevertheless, BMD is widely accepted as a suitable outcome for clinical trials of osteoporosis treatments, based on numerous published studies that have demonstrated a significant correlation between BMD and fracture incidence. In addition, denosumab has been shown to reduce the incidence of new vertebral and hip fractures in women with post-menopausal osteoporosis in several studies. The Canadian Expert Drug Advisory Committee (CEDAC) recommended in 2011 that denosumab be reimbursed for women with post-menopausal osteoporosis who would otherwise be eligible for jurisdictional funding for oral bisphosphonates, but for whom bisphosphonates are contraindicated due to hypersensitivity or abnormalities of the esophagus, and who have at least two of the following: age > 75 years; a prior fragility fracture; or a T-score ≤ –2.5. The recommendation was based on the fact that, in one DB RCT in post-menopausal women with low BMD, denosumab achieved a statistically significantly greater reduction in the incidence of new vertebral and hip fractures compared with placebo. It is uncertain whether the clinical benefits of denosumab on BMD observed in men in ADAMO would translate to a corresponding reduction in fracture risk as in post-menopausal women, although it is likely that denosumab would have a similar clinical benefit in terms of fracture reduction in men.

Another limitation of the ADAMO study is related to generalizability. Although the trial population in ADAMO did have a high risk of fracture, patients who were at the highest risk of fracture (based on their BMD values or fracture history) were excluded from the trial, and the proportion of patients in the trial who had sustained a prior fracture was smaller than would be expected in clinical practice. Therefore, the ADAMO trial population comprised patients who were at a lower risk of sustaining a fracture than the population likely to be seen in clinical practice in Canada, according to the clinical expert consulted by CDR reviewers. In addition, patients with various comorbid conditions commonly seen in clinical practice were excluded from the study, including those with impaired renal function, bilateral hip replacement, known HIV, hepatitis B or C, and recent malignancy. The exclusion of patients who received bisphosphonate treatment within the last two years is not representative of current clinical practice, as bisphosphonates are first-line therapy for men with low BMD. This is potentially important when interpreting the relative efficacy of denosumab compared with other drugs, because it is possible that patients treated recently with bisphosphonates who are switched to denosumab treatment could experience a smaller improvement in BMD compared with previously untreated patients. Indeed, evidence in post-menopausal women from the STAND trial shows that patients who received alendronate or equivalent for at least six months prior to screening experienced a change from baseline in lumbar spine BMD with denosumab that reached statistical significance, but that was of lower magnitude compared with the other denosumab trials that did not enroll patients with recent bisphosphonate experience.

4.2 Interpretation of Results

4.2.1 Efficacy

a) Interpretation of the findings

Results from the ADAMO study demonstrate the superiority of denosumab over placebo in order to improve lumbar spine BMD after 12 months of treatment in men with low BMD. The mean change from baseline in patients receiving denosumab reached 5.7% (95% CI, [redacted]), which was considered clinically significant, as experience from the clinical expert consulted by CDR suggests an MCID of 3% for lumbar spine BMD. The small improvement of < 1% (95% CI, [redacted]) in the placebo group in ADAMO likely was the result of concomitant administration of calcium and vitamin D to these patients. The manufacturer elected to use measures at the lumbar spine for the primary outcome of change in BMD, because this site is primarily trabecular and therefore is more metabolically active and more responsive to treatment.[8] Indeed, the clinical expert consulted by CDR indicated that total hip and femoral neck show a slower response to treatment; nevertheless, the effects of denosumab were also superior to placebo for these secondary outcomes, although the magnitude of the between-group difference at these other anatomical sites was smaller.

Long-term maintenance of denosumab effectiveness on BMD was documented during the ADAMO subsequent 12-month open-label phase, during which all patients received denosumab. BMD continued to increase in patients already receiving denosumab, with a change in lumbar spine BMD increasing from 5.7% (95% CI, [redacted]) at 12 months to reach 8.0% (95% CI, [redacted]) after 24 months of treatment. Patients transitioning from placebo to denosumab experienced gains in BMD that were of similar magnitude to those experienced by patients receiving denosumab in the DB phase (5.7%; 95% CI, [redacted]). However, there are no data to inform on the effectiveness of denosumab beyond 24 months, despite the fact that most patients require long-term treatment over many years.

b) Additional relevant literature

There is a lack of evidence with which to directly compare denosumab with other drugs used for the treatment of osteoporosis in men. In order to inform this evidence gap, CDR reviewed available indirect evidence. A literature review conducted by CDR to identify relevant published indirect comparisons did not yield any IDCs. However, the CDR reviewers did critically appraise two IDCs submitted by the manufacturer for the purpose of this review, in which the comparative efficacy of denosumab and zoledronic acid for increasing BMD in men with osteoporosis was assessed (see further details in APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS). The first IDC compared denosumab with zoledronic acid in a two-step loop. The first step compared denosumab with alendronate through placebo as the common comparator, and the second step was through the direct comparison between alendronate and zoledronic acid. The second IDC compared denosumab with zoledronic acid in a one-step loop that had placebo as the only common comparator. The results of the two IDCs were consistent in demonstrating that there are no statistically significant differences between the effects of denosumab and zoledronic acid on the change in BMD after 12 months in the hip, femoral neck, and trochanter. In one of the two IDCs, denosumab was associated with a small but statistically significantly greater improvement in BMD versus zoledronic acid only in the lumbar spine, but no such difference was detected in the other IDC. The small number of studies available and the correspondingly small number of included patients mean that the effects of heterogeneity among studies on the comparative efficacy of treatment are highly uncertain. Therefore, the overall results of the IDCs are consistent with the conclusion that there is no evidence of any clinically relevant differences in the increase in BMD associated with denosumab and zoledronic acid treatment in men with osteoporosis.

The two IDCs submitted by the manufacturer did not compare denosumab with all treatment options available to men with osteoporosis, notably the oral bisphosphonates alendronate and risedronate. However, comparison between denosumab and oral bisphosphonates is less relevant than comparison between denosumab and zoledronic acid, because oral bisphosphonates are considered first-line treatment options, whereas the injectable drugs denosumab and zoledronic acid will likely be considered second-line options, according to the clinical expert consulted by CDR. Similarly, teriparatide was not considered to be a relevant comparator, because this is a third-line injectable drug reserved for patients for whom initial therapy is insufficient, must be injected once daily, and is substantially more expensive than other treatments.

4.2.2 Harms

a) Interpretation of the findings

Denosumab is approved for six indications and has been in use since 2010, and the overall harms in ADAMO results did not raise any new safety concerns. Additional safety data included the ADAMO open-label phase (Appendix 6), which showed that the overall frequency and type of AEs observed in the DB phase did not change over the long term in patients who continued denosumab through 24 months, as well as in patients who transitioned from placebo to denosumab for a 12-month open-label treatment period.

Mortality as well as the overall incidence of SAEs during ADAMO did not differ significantly between denosumab and placebo, and were not higher than would be expected in this patient population in clinical practice according to the clinical expert consulted by CDR. The most commonly reported SAEs for both treatments were infrequent (< 2.5%). Three patients reported prostate cancer throughout the ADAMO trial, all in the denosumab treatment group; however, the clinical expert consulted by CDR highlighted the high prevalence of this malignancy in this patient population. The proportion of patients experiencing AEs was also similar between denosumab and placebo. The most common AEs included

back pain, arthralgia, and nasopharyngitis. Limited proportions of patients discontinued due to AEs in the denosumab treatment group, suggesting adequate tolerability.

Some AEs of particular interest were identified by CDR based on the denosumab mechanism of action and Health Canada warnings, which have been issued with regard to the risks of hypocalcemia, infections, dermatologic AEs, osteonecrosis of the jaw, atypical femur fractures, and malignancies.[5] There were no reports of osteonecrosis of the jaw, atypical femur fractures, fracture healing complications, or hypocalcemia throughout the ADAMO study duration. Results for other notable AEs are characterized by a low number of events reported in both treatment groups. The only exception pertains to infections, which were experienced by 20% of patients in both treatment groups.

b) Additional relevant literature

No data are available to directly compare the potential harms of denosumab versus other active treatment options for men with osteoporosis. Potential harms were not analyzed in the two IDCs that were available to CDR to compare the safety of denosumab with that of zoledronic acid. However, the available evidence (i.e., the proportions of patients experiencing AEs and SAEs in the included studies used in the IDCs) suggests that denosumab and zoledronic acid likely do not have markedly different safety profiles. Nevertheless, given the limitations of the indirect comparisons (most notably the small number of studies and included patients), there is a high degree of uncertainty related to interpreting the comparative safety profile associated with denosumab compared with zoledronic acid.

c) Other considerations

According to the patient input received by CDR, it is expected that patients who are unable to tolerate oral bisphosphonates due to gastrointestinal disorders, problems swallowing or who suffer from other AEs with bisphosphonates will experience fewer AEs with the use of an injectable drug such as denosumab, thereby increasing the probability of adherence to treatment and consequently, improved effectiveness. Indeed, there were no reports of gastrointestinal disorders with the use of denosumab throughout the ADAMO trial. For these patients, other injectable options, specifically zoledronic acid, would be equally appropriate therapeutic alternatives.

5. CONCLUSIONS

The results of the ADAMO study demonstrated the superiority of denosumab over placebo for improving lumbar spine BMD after 12 months of treatment in men with low BMD. In the open-label extension phase, denosumab continued to be effective in improving BMD up to 24 months. However, the trial did not provide evidence to inform on the effects of denosumab on clinical outcomes such as fractures and quality of life. There were no reports of osteonecrosis of the jaw, atypical femur fractures, fracture healing complications, or hypocalcemia. Few patients experienced dermatologic AEs or malignancies, and similar proportions of patients developed infections in both treatment groups. The generalizability of the results of ADAMO are limited by the fact that the trial population had a slightly lower risk of fracture than that seen in clinical practice, as well as by the exclusion of patients with commonly seen comorbid conditions, and by the exclusion of patients who had received recent bisphosphonate treatment. The results of two indirect comparisons submitted by the manufacturer in which the efficacy of denosumab was compared with zoledronic acid were consistent with the conclusion that denosumab is at least as effective as zoledronic acid for increasing BMD in men with osteoporosis.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group Supplying Input

CADTH received input from one patient group — Osteoporosis Canada (OC) — to support the CADTH Common Drug Review (CDR) evaluation of denosumab for men with osteoporosis. OC is a national organization that serves people who have, or are at risk for, osteoporosis and osteoporotic fractures. The organization works to educate, empower, and support individuals and communities in the risk reduction and treatment of osteoporosis and fractures. OC provides information to patients, health care professionals, and the public. At the time of submission, OC was receiving unrestricted educational grants from Amgen Canada Inc., Eli Lilly Inc., and Merck Canada Inc.

2. Condition and Current Therapy-Related Information

OC gathered information from the Osteoporosis Canada 2010 Clinical Practice Guidelines and the Canadian Multicentre Osteoporosis Study 2007. The OC submission also included anecdotal information from patients currently on denosumab who have failed oral treatment options.

At least one in five men will experience a fracture from osteoporosis during their lifetime. In Canada, about 7,500 men sustain hip fractures yearly and are more likely to die of complications from a hip fracture than women: 37% of men who suffer a hip fracture will die within the following year, compared with 28% of women. The care gap for men is greater than for women. In general, fewer than 20% of fracture patients receive assessment and treatment for underlying osteoporosis; for men, that percentage is less than 10%. Fragility fractures are the main consequence of osteoporosis and their effects can be devastating (loss of independence, decreased mobility, isolation, depression, and, in some cases, death).

The OC submission reported that men do not have equal access to currently available treatment for osteoporosis compared with women, considering that denosumab is reimbursed for women with post-menopausal osteoporosis. Bisphosphonates have been the most commonly prescribed medications for men with osteoporosis; however, some patients do not tolerate oral bisphosphonates. Those who find oral bisphosphonates inconvenient do so because it has to be administered the first thing in the morning, on an empty stomach before breakfast or that first cup of coffee, or because they need to stay upright during this period. For men with gastrointestinal disorders, problems swallowing, or who suffer other side effects, oral bisphosphonates are not safe, and therefore not an option.

The impact of fractures on caregivers is significant and can be financial or personal, but is usually associated with emotional stress for all involved. The fracture patient may be unable to perform many routine personal care activities, including those that embarrass and humiliate both the patient and the caregiver. Many patients say that the emotional stress can be more significant than having to deal with the excruciating pain of a broken bone.

3. Related Information About the Drug Being Reviewed

It is expected that denosumab will be the best option for a subgroup of patients who are unable to tolerate oral drugs, to increase bone mass and reduce fracture risk at the hip, spine, and wrist. As the administration of denosumab is non-oral, it is expected that patients who are unable to tolerate oral drugs will have fewer adverse side effects associated with oral options, thereby increasing the probability of these individuals to live full, vital, and fragility fracture–free lives. In one-on-one interviews, patients on denosumab expressed their preference for its administrations schedule, further increasing the likelihood of patients staying on this option. Overall, access to denosumab is expected to provide patients with more tolerable treatment, higher adherence to treatment, and better health outcomes overall.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 11, 2015
Alerts:	Weekly search updates until (August 19, 2015)
Study Types:	Randomized controlled trials; controlled clinical trials
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(prolia* or denosumab* or Pralia or Ranmark or Xgeva or AMG162 or AMG 162).ti,ot,ab,sh,rn,hw,nm.
2	(615258-40-7 or "615258407" or 61525840 7 or "6152584 07" or 615258 407).rn.
3	1 or 2
4	3 use pmez
5	*denosumab/
6	prolia/
7	(prolia* or denosumab* or Pralia or Ranmark or Xgeva or AMG162 or AMG 162).ti,ab.
8	5 or 6 or 7
9	8 use oemezd
10	4 or 9
11	10 not conference abstract.pt.
12	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
13	Randomized Controlled Trial/
14	Randomized Controlled Trials as Topic/
15	"Randomized Controlled Trial (topic)"/
16	Controlled Clinical Trial/
17	Controlled Clinical Trials as Topic/
18	"Controlled Clinical Trial (topic)"/
19	Randomization/
20	Random Allocation/
21	Double-Blind Method/
22	Double Blind Procedure/
23	Double-Blind Studies/
24	Single-Blind Method/
25	Single Blind Procedure/
26	Single-Blind Studies/
27	Placebos/
28	Placebo/
29	Control Groups/
30	Control Group/
31	(random* or sham or placebo*).ti,ab,hw.
32	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
33	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
34	(control* adj3 (study or studies or trial*)).ti,ab.
35	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
36	allocated.ti,ab,hw.
37	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
38	or/12-37
39	11 and 38
40	(men or man or male*).ti,ab.
41	exp male/
42	exp Men/
43	40 or 41 or 42

MULTI-DATABASE STRATEGY	
#	**Searches**
44	39 and 43
45	exp animals/
46	exp animal experimentation/ or exp animal experiment/
47	exp models animal/
48	nonhuman/
49	exp vertebrate/ or exp vertebrates/
50	animal.po.
51	or/45-50
52	exp humans/
53	exp human experimentation/ or exp human experiment/
54	human.po.
55	or/52-54
56	51 not 55
57	44 not 56
58	remove duplicates from 57
40	(men or man or male*).ti,ab.
41	exp male/
42	exp Men/
43	40 or 41 or 42
44	39 and 43
45	exp animals/
46	exp animal experimentation/ or exp animal experiment/
47	exp models animal/
48	nonhuman/
49	exp vertebrate/ or exp vertebrates/
50	animal.po.
51	or/45-50
52	exp humans/
53	exp human experimentation/ or exp human experiment/
54	human.po.
55	or/52-54
56	51 not 55
57	44 not 56
58	remove duplicates from 57

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	February 2015
Keywords:	Prolia, denosumab, men, osteoporosis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Nakamura et al.[16]	Inappropriate population

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 9: EFFICACY OUTCOME RESULTS

	ADAMO	
	Denosumab N = 117	Placebo N = 118
A. Vertebral, Hip, and Other Non-Vertebral Fractures		
No data reported		
B. Per cent Change from Baseline in BMD		
Lumbar Spine BMD[a]		
Per Cent Change from Baseline at Month 6		
LS mean	4.3	0.9
95% CI	[redacted]	[redacted]
Difference from Placebo – Primary Efficacy Population, LOCF		
LS mean	3.4	
95% CI	[redacted]	
P value	*P* < 0.0001	
Difference from Placebo – PP Population, LOCF		
LS mean	3.4	
95% CI	[redacted]	
P value	*P* < 0.0001	
Per Cent Change from Baseline at Month 12		
LS mean	5.7	0.9
95% CI	[redacted]	[redacted]
Difference from Placebo – Primary Efficacy Population, LOCF		
LS mean	4.8	
95% CI	4.0 to 5.6	
P value	*P* < 0.0001	
Difference from Placebo – PP Population, LOCF		
LS mean	5.0	
95% CI	[redacted]	
P value	*P* < 0.0001	
Total Hip BMD[b]		
Difference from Placebo at Month 12		
Estimate	2.0	
95% CI	[redacted]	
P value	*P* < 0.0001	
Femoral Neck BMD[b]		
Difference from Placebo at Month 12		
Estimate	2.2	

	ADAMO	
	Denosumab N = 117	Placebo N = 118
95% CI	[redacted]	
P value	*P* < 0.0001	
C. Health-Related Quality of Life		
No data reported		
D. Hospitalizations		
No data reported		

BMD = bone mineral density; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; PP = per protocol.

[a] The primary outcome in the ADAMO study was the mean per cent change in lumbar spine BMD at 12 months.

[b] In the placebo group, total of 119 patients contributed data to the secondary outcome analysis.

Source: Clinical Study Report, pp. 103, 105.[8]

TABLE 10: MORTALITY AND OTHER SERIOUS ADVERSE EVENTS

Number of Patients with Harms Outcome	ADAMO	
	Denosumab N = 120	Placebo N = 120
Mortality		
n (%)	**1 (0.8)**	**1 (0.8)**
Most frequently reported reason — ≥ 1 patient in at least one treatment group, n (%):		
MI	1 (0.8)	0
Basilar artery thrombosis	0	1 (0.8)
Treatment-emergent SAEs		
n (%)	**11 (9.2)**	**10 (8.3)**
Most frequently reported SAEs — ≥ 1 patient in at least one treatment group, n (%):		
Prostate cancer	3 (2.5)	0
Arterial thrombosis limb	2 (1.7)	0
Pancreatitis acute	1 (0.8)	1 (0.8)
Peripheral ischemia	1 (0.8)	1 (0.8)
Acute MI	1 (0.8)	0
Chest pain	1 (0.8)	0
Cholecystitis	1 (0.8)	0
Injury	1 (0.8)	0
MI	1 (0.8)	0
Post procedural complication	1 (0.8)	0
Road traffic accident	1 (0.8)	0
Spinal column stenosis	1 (0.8)	0
Vascular pseudo-aneurysm	1 (0.8)	0
AF	0	1 (0.8)
Basilar artery thrombosis	0	1 (0.8)
Cerebral hemorrhage	0	1 (0.8)
Ligament rupture	0	1 (0.8)
Meniscus lesion	0	1 (0.8)
Osteoarthritis	0	1 (0.8)
Pneumonia	0	1 (0.8)
Prostatic adenoma	0	1 (0.8)
Retinal detachment	0	1 (0.8)
Skull malformation	0	1 (0.8)
Vitreous hemorrhage	0	1 (0.8)

AF = atrial fibrillation; MI = myocardial infarction; SAEs = serious adverse events.
Source: Clinical Study Report, pp. 118-9.[8]

TABLE 11: NOTABLE HARMS

Number of Patients with Harms Outcome	ADAMO	
	Denosumab N = 120	Placebo N = 120
Harms of Particular Interest[a], n (%)		
Acute pancreatitis	1 (0.8)	1 (0.8)
Atypical femur fractures[b]	0	0
Cardiac disorders		
AEs	[redacted]	3 (2.5)
SAEs	2 (1.7)	1 (0.8)
Eczema[b]	2 (1.7)	0
Fracture healing complications	0	0
Hypersensitivity	3 (2.3)	3 (2.5)
Hypocalcemia[b]	0	0
Infection[b]		
AEs	24 (20.0)	24 (20.0)
SAEs	0	1 (0.8)
Malignancy	4 (3.3)	0
Osteonecrosis of the jaw[b]	0	0
Skin infection[b]		
AEs	0	1 (0.8)
SAEs	0	0
Vascular disorders		
AEs	[redacted]	[redacted]
SAEs	[redacted]	[redacted]

AE = adverse event; SAE = serious adverse event.
[a] Treatment-emergent harms identified by the manufacturer based on their possible association with antiresorptive activity or RANKL inhibition, reactivity to monoclonal antibody administration, or because of results from previous clinical studies.
[b] Harms outcomes pre-specified by CADTH in the systematic review protocol.

[redacted]

Source: Clinical Study Report, pp. 121-5.[8]

TABLE 12: ADVERSE EVENTS

Number of Patients with Harms Outcome	ADAMO	
	Denosumab N = 120	Placebo N = 120
AEs		
n (%)	**86 (71.7)**	**84 (70.0)**
Most Frequently Reported AEs — ≥ 2% in at Least 1 Treatment Group, n (%):		
Back pain	10 (8.3)	8 (6.7)
Arthralgia	8 (6.7)	7 (5.8)
Nasopharyngitis	8 (6.7)	7 (5.8)
Osteoarthritis	4 (3.3)	2 (1.7)
Angina pectoris	4 (3.3)	0
Hypercholesterolemia	3 (2.5)	0
Muscle spasms	3 (2.5)	0
Prostate cancer	3 (2.5)	0
Myalgia	2 (1.7)	5 (4.2)
Cataract	2 (1.7)	3 (2.5)
Diarrhea	2 (1.7)	3 (2.5)
Pain in extremity	2 (1.7)	3 (2.5)
Headache	1 (0.8)	5 (4.2)
Hypertension	1 (0.8)	5 (4.2)
Influenza	1 (0.8)	4 (3.3)
Musculoskeletal pain	1 (0.8)	4 (3.3)
Cough	1 (0.8)	3 (2.5)
Constipation	0	7 (5.8)
Abdominal pain upper	0	3 (2.5)
Procedural pain	0	3 (2.5)
WDAEs		
n (%)	**3 (2.5)**	**0**
Most Frequently Reported Reasons — ≥ 1 Patient in at Least 1 Treatment Group, n (%):		
Prostate cancer	1 (0.8)	0
Traffic accident and resultant traumatic injuries	1 (0.8)	0
Increased frequency of upper respiratory tract infections	1 (0.8)	0

AE = adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report, pp. 118, 127.[8]

APPENDIX 5: VALIDITY OF BONE MINERAL DENSITY AS OUTCOME MEASURE

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim

To review the validity of bone mineral density (BMD) as a surrogate for risk of bone fractures in patients with osteoporosis.

Findings

BMD is often used to define osteoporosis, with a 1994 World Health Organization categorization based on T-scores (the number of standard deviations [SDs] above or below the mean value for young adults):[17,18]

- normal: T-score –1 or higher
- osteopenia: T-score between –1 and –2.5
- osteoporosis: T-score –2.5 or less.

In clinical trials, BMD is often used as a surrogate outcome for risk of future fractures. The value of using BMD as a fracture predictor was extensively evaluated in the literature. For example, Cranney et al. examined a cohort of 16,505 post-menopausal women aged 50 years or older (mean 65 years) whose lumbar spine and proximal femur BMD results were contained in the Manitoba Bone Density Program database; 98% of the women were Caucasian.[19] A study objective was to determine fracture rates in relation to BMD after a mean follow-up period of three years. Results showed that fracture rates were highest among women with osteoporotic T-scores (26.2 per 1,000 person-years versus 14.3 for those with osteopenic and 8.2 for those with normal BMD results), although only 40% of the fractures actually occurred in this patient subgroup as fewer women in the cohort fell into the osteoporotic group. The overall odds ratios for fracture for women with osteoporotic or osteopenic BMD values compared with women with normal BMD values were:

- osteoporotic BMD values: 3.52 to 6.85 per 1,000 person-years
- osteopenic BMD values: 1.83 to 2.59 per 1,000 person-years.

Another example was the Study of Osteoporotic Fractures (SOF) that investigated the association between vertebral fractures and BMD in a cohort of white women aged 65 to 99 years (mean 68.8 years) from four US centres over the period 1986 to 2004.[20] Of the 9,704 women recruited, 2,680 attended clinic visits for a mean of 15 years. In this group, both prevalent and incident vertebral fractures were identified. Results showed that women with osteoporosis based on BMD T-scores had the highest incidence of vertebral fracture as compared with women with BMD results in the osteopenic or normal range. Risk of vertebral fracture was also high for women with prevalent vertebral fractures at baseline regardless of BMD. Women with both a prevalent vertebral fracture and osteoporotic BMD values had a 50% absolute risk of incident vertebral fracture (versus those with no prevalent fracture and normal BMD values whose absolute risk was 9%). The authors noted that a single measure of BMD predicted incident vertebral fractures over the 15-year study period. However, independent of BMD, identification of prevalent vertebral fractures was a useful predictor.

In an earlier report, Cauley et al. investigated the connection between BMD at the hip and femoral neck and incident non-spinal fractures using SOF cohort data from post-menopausal Caucasian (n = 7,334) and black (n = 636) women at a mean follow-up of 6.5 years (SD 1.5).[21] Black women are known to have a lower risk of fracture and therefore the predictive value of BMD was of interest. Results showed that a 1- SD decrease in femoral neck BMD was associated with a 37% increased risk of fracture in black women (relative risk [RR] 1.37; 95% confidence interval [CI], 1.08 to 1.74) and a 49% increase in white women (RR 1.49; 95% CI, 1.40 to 1.58); however, adjustment for body weight and other risk factors weakened the associations, particularly for black women.[21]

A group of 29 international osteoporosis experts published risk assessment tools to predict fractures using clinical risk factors (CRFs) as well as BMD.[22] Nine population-based studies provided the data, comprising 46,340 patients (68% women) over 190,000 person-years. The unit of measurement, gradient of risk (GR), represented the increase in fracture risk per SD increase in risk score; the higher the GR, the more accurately the factor is predicting the risk. Using CRFs alone, BMD alone, and the combination, GRs were calculated for prediction of hip fracture and other major osteoporotic fractures (clinical spine, forearm, and proximal humerus). For hip fracture, using CRFs alone provided a GR of 2.1 per SD at age 50, while using BMD alone provided a GR of 3.7 per SD, whereas the combination of BMD and CRFs was the best predictor, providing a GR of 4.2 per SD. For other osteoporotic fractures, results were less dramatic; a GR of 1.4 per SD at age 50 was calculated for CRFs alone, BMD alone, and the combination.[22]

A 2005 meta-analysis led by Johnell in Sweden aimed to quantify the relationship between BMD and fracture risk, and also to determine how well BMD could predict fracture when considering patient age, sex, time since last BMD assessment, and BMD absolute value.[23] Data were drawn from 12 cohort studies (n = 38,973; 9,891 men and 29,082 women) and follow-up extended to 16.3 years (168,366 person-years). With respect to the BMD/fracture relationship, results showed femoral neck BMD to be a strong predictor of hip fractures in both men and women, i.e., at age 65, for each SD decrease in BMD, the risk ratio increased by 2.94 (95% CI, 2.02 to 4.27) in men and 2.88 (95% CI, 2.31 to 3.59) in women. Results for non-hip fractures and osteoporotic fractures were less impressive, i.e., at age 65, for each SD decrease in BMD, the risk ratio increased by 1.41 (95% CI, 1.33 to 1.51) in men and 1.38 (95% CI, 1.28 to 1.48) in women. For any fracture, the GR increased with age.[23]

The National Osteoporosis Risk Assessment (NORA) is a cohort study of 200,160 post-menopausal women from 34 US states with no previous osteoporosis diagnosis. In 2001, Siris et al. examined the association between peripheral BMD (heel, finger, or forearm) and fracture rates at 12-month follow-up for the 164,000 women with adequate data.[24] According to BMD findings, 7% had osteoporosis, 40% had osteopenia, and 53% were normal. Outcome analysis showed that osteoporotic BMD was associated with a fracture rate four times that of normal BMD (95% CI, 3.6 to 4.5) and osteopenia was associated with a 1.8-fold higher rate (95% CI, 1.5 to 2.2).[24]

An early influential meta-analysis of the ability of BMD to predict fracture was performed by Marshall et al. and funded by the Swedish Council on Technology Assessment in Health Care.[25] Only studies enrolling older women were included. Eleven prospective cohort studies published between 1985 and 1994 were analyzed, these covering 90,000 person-years of data and more than 2,000 fractures, with follow-up ranging from 1.8 to 24 years. BMD was performed at a number of body sites, including radius, spine, calcaneus, and hip. The main outcome measure was RR of fracture for a BMD decrease that was 1 SD below the age-adjusted mean. Results showed that all measuring sites had similar predictive abilities

(RR 1.5; 95% CI, 1.4 to 1.6) for a decrease in BMD, except for measurement at the spine for predicting vertebral fractures (RR 2.3), and measurement at the hip for predicting hip fractures (RR 2.6).[25]

Thus, although BMD can serve as a useful predictor of fracture risk, the issue is complex. This is mainly due to the fact that as most post-menopausal women in a population fall into the osteopenic or normal range, more fractures occur in this group than in the osteoporotic group. Also, BMD alone is not as useful a predictor as are a combination of risk-related factors such as age, prior fracture, and BMD. In addition to the studies described above, two further examples illustrating these points include:

- Pasco et al.: Australian researchers examined a population-based random sample of 616 post-menopausal women over a median of 5.6 years.[26] Only 14% had osteoporotic BMD values, whereas 48% had osteopenic and 38% had normal total hip BMD values. Although fracture incidence was highest in those with osteoporosis, just 27% of all fractures arose from this group, whereas 73% occurred in women without osteoporosis (osteopenia 57%; normal BMD 16%). Increased fracture risk was independently related to decreasing BMD, increasing age, and prior fracture. The RR for fracture increased 65% for each SD decrease in BMD (RR 1.65; 95% CI, 1.32 to 2.05), increased 3% for every year of age (RR 1.03; 95% CI, 1.01 to 1.06) and doubled with prevalent fracture (RR 2.01; 95% CI, 1.40 to 2.88).[26]
- Sornay-Rendu et al.: Researchers in France analyzed the vertebral and non-vertebral fracture outcomes of a cohort of post-menopausal women enrolled in the Os des Femmes de Lyon (OFELY) cohort study (n = 671).[27] After nine years of follow-up, 44% of those with fractures had osteoporotic BMD values, whereas 48% were osteopenic and 8% had normal BMD. The osteopenic group was of particular interest in this study, and although low BMD (T-score 2.0 to 2.5) was found to be associated with fracture risk, so were age, prior fracture, and bone alkaline phosphatase.

Compounding the complexity of the BMD/fracture risk relationship are observations that the effects of antiresorptive drugs on BMD may not be directly and closely linked to fracture reduction. For example, French researchers analyzed data suggesting that antiresorptive drugs decrease fractures by increasing BMD, and concluded that only a small proportion of the risk reduction in vertebral and non-vertebral fractures observed with antiresorptive drug therapy could be explained by the increase in BMD.[28] Their conclusions were based in part on a 2002 meta-analysis of 12 trials of osteoporosis antiresorptive therapies, BMD, and vertebral fracture that found that drug-induced increases in BMD account for only a small part of observed reduction in fracture risk.[29] Similar findings were reported by Watts et al. in a combined analysis of three risedronate trials with respect to vertebral and non-vertebral fractures.[30] Other researchers have found variation in the effect of antiresorptive drugs, with some showing greater effects on BMD and fracture than others.[31]

APPENDIX 6: SUMMARY OF A LONG-TERM EXTENSION STUDY

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim
To summarize data from the extension period of the ADAMO trial.[32]

Findings
ADAMO extension was a non-randomized, single-group, 12-month, open-label extension period immediately following the 12-month double-blind period. During the extension period all enrolled patients (independent of randomization) received 60 mg subcutaneous (SC) denosumab in single doses at the first and sixth months of the extension study (Q6M). All patients received daily supplements of calcium (≥ 1,000 mg elemental calcium) and vitamin D (≥ 800 IU) through month 12 of the extension period. Final study assessments were conducted at month 12 of the extension study (end-of-study visit).

The efficacy analysis set comprised all patients who entered the open-label phase. Observed data were used for the efficacy analyses, including patients who had a non-missing study baseline and a non-missing evaluation at the time point under consideration. The means and 95% confidence intervals (CIs) of per cent changes from baseline in bone mineral density (BMD) were estimated at months 18 and 24 by an analysis of covariance (ANCOVA) model with treatment as main effect and minimum baseline BMD T-score (stratification factor) as covariate.

Adverse events in the open-label phase were summarized by treatment group (long-term, crossover). Treatment-emergent, treatment-related, serious, serious treatment-related, and fatal adverse events, as well as adverse events leading to investigational product discontinuation and/or study discontinuation, were summarized by preferred term and system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Laboratory data were summarized descriptively by visit for the actual values and changes from baseline. Laboratory data also were summarized using shifts in recorded values from baseline to worst on-study value. Vital signs were summarized descriptively by visit for the recorded values and changes from baseline. Anti-denosumab antibody results were listed for each patient and summarized.

Patient Disposition
In total, 242 patients were initially enrolled and randomized to receive either placebo (N = 121) or denosumab (N = 121) during the 12-month double-blind phase of the study (Table 13).
Two-hundred twenty-eight patients (228/242 = 94%) completed the double-blind phase and entered the open-label phase, one of whom (crossover) never received denosumab in this phase but remained on study and completed study.

Of the 228 patients who entered the open-label phase, 96% (219/228) (105/111 [95%] long-term, 114/117 [97%] crossover) completed this phase (Table 13). For the overall study, of the 242 initially randomized patients, 90.5% (219/242) (105/121 [87%] denosumab/long-term, 114/121 [94%] placebo/crossover) completed 24 months of study participation.

TABLE 13: SUMMARY OF PATIENT DISPOSITION

	Placebo/Denosumab 60 mg Q6M N (%)	Denosumab/Denosumab 60 mg Q6M N (%)
Randomized	121	121
Entered open-label extension	117 (96.7)	111 (91.7)
Completed 24 months of study	114 (94.2)	105 (86.8)
Completed study drug	[redacted]	[redacted]
Discontinued study drug	[redacted]	[redacted]
Never received study drug	[redacted]	[redacted]
Discontinued before completing 24 months of study	3 (2.5)	6 (5.0)
Completed study drug	[redacted]	[redacted]
Discontinued study drug	[redacted]	[redacted]
Never received study drug	[redacted]	[redacted]

Q6M = single doses at the first and sixth months.
Source: ADAMO Clinical Study Report.[32]

Baseline demographics and baseline characteristics are summarized in Table 14. For the long-term (denosumab/denosumab) and the crossover (placebo/denosumab) groups, respectively, age was long-term 65.0 (10.2) and 65.1 (9.2) years and Caucasian patients presented 100% and 88.9%.

TABLE 14: SUMMARY OF PATIENT BASELINE CHARACTERISTICS

	Placebo/Denosumab 60 mg Q6M N (%)	Denosumab/Denosumab 60 mg Q6M N (%)
Entered open-label extension	117 (100)	111 (100)
Ethnic group		
White or Caucasian	104 (89)	111 (100)
Hispanic or Latino	9 (7.7)	0
Asian	2 (1.7)	0
Black or African American	1 (0.9)	0
Native Hawaiian or Other Pacific Islander	1 (0.9)	0
Age (years), mean (SD)	65.1 (9.2)	65.0 (10.2)
BMI (kg/m^2), mean (SD)	[redacted]	[redacted]
Minimum BMD T-score at lumbar spine or total hip		
≤ –2.5	[redacted]	[redacted]
> –2.5	[redacted]	[redacted]
BMD T-score, mean (SD)		
Lumbar spine	–2.0 (1.0)	–1.9 (1.1)
Total hip	–1.4 (0.7)	–1.5 (0.6)
Femoral neck	–1.9 (0.6)	–1.9 (0.6)
Trochanter	–1.3 (0.7)	–1.2 (0.7)
Distal 1/3 radius	–1.7 (1.2)	–1.3 (1.3)

BMD = bone mineral density; Q6M = single doses at the first and sixth months; SD = standard deviation.
Source: ADAMO Clinical Study Report.[32]

Efficacy Results

Efficacy results are summarized in Table 15. In the open-label phase, for the efficacy analysis set of patients who entered the open-label phase (N = 111 long-term, 117 crossover), BMD at the lumbar spine, total hip, femoral neck, hip trochanter, and distal radius continued to increase from month 12 to month 24 in the long-term group. In this group, mean per cent increases from baseline were 8.0%, 3.4%, 3.4%, 4.6%, and 0.7% for lumbar spine, total hip, femoral neck, hip trochanter, and distal radius, respectively, at month 24 compared with 5.8%, 2.3%, 2.2%, 3.2%, and 0.6% at month 12.

In the crossover group, increases from month 12 to month 24 were similar to those observed in the long-term group from baseline to month 12 during the initial denosumab treatment. In this group, mean per cent changes from baseline were 5.7%, 2.0%, 1.8%, 2.7%, and 0.6% for lumbar spine, total hip, femoral neck, hip trochanter, and distal radius, respectively, at month 24 compared with 0.8%, 0.3%, –0.1%, 0.8%, and –0.3% at month 12.

TABLE 15: SUMMARY OF EFFICACY RESULTS

Per Cent Change From Baseline in BMD Least Square (95% Confidence Interval)	Placebo[a]/ Denosumab[b] 60 mg Q6M N = 117	Denosumab[a]/ Denosumab[b] 60 mg Q6M N = 111	Difference From Placebo
Lumbar spine			
Month 6 (double-blind period)	0.9 (0.3 to 1.4)	4.3 (3.83 to 4.9)	[redacted]
Month 12 (double-blind period)	0.8 (0.2 3 to 1.4)	5.8 (5.23 to 6.3)	[redacted]
Month 24 (open-label period)	5.7 (5.03 to 6.4)	8.0 (7.33 to 8.7)	Not reported
Total hip			
Month 6 (double-blind period)	0.1 (–0.23 to 0.5)	1.6 (1.33 to 2.0)	[redacted]
Month 12 (double-blind period)	0.3 (–0.13 to 0.7)	2.3 (1.93 to 2.8)	[redacted]
Month 24 (open-label period)	2.0 (1.63 to 2.4)	3.4 (2.93 to 3.8)	Not reported
Femoral neck			
Month 6 (double-blind period)	0.0 (–0.53 to 0.5)	1.7 (1.13 to 2.2)	[redacted]
Month 12 (double-blind period)	–0.1 (–0.73 to 0.5)	2.2 (1.53 to 2.8)	[redacted]
Month 24 (open-label period)	1.8 (1.13 to 2.5)	3.4 (2.73 to 4.2)	Not reported
Trochanter			
Month 6 (double-blind period)	0.2 (–0.33 to 0.7)	1.8 (1.33 to 2.3)	[redacted]
Month 12 (double-blind period)	0.8 (0.13 to 1.4)	3.2 (2.53 to 3.8)	[redacted]
Month 24 (open-label period)	2.7 (2.03 to 3.4)	4.6 (3.93 to 5.3)	Not reported
Distal 1/3 radius			
Month 6 (double-blind period)	–0.3 (–0.83 to 0.2)	0.1 (–0.43 to 0.6)	[redacted]
Month 12 (double-blind period)	–0.3 (–0.83 to 0.2)	0.6 (0.13 to 1.1)	[redacted]
Month 24 (open-label period)	0.6 (0.13 to 1.1)	0.7 (0.23 to 1.2)	Not reported

BMD = bone mineral density; Q6M = single doses at the first and sixth months.
[a] During the double-blind period.
[b] During the open-label period.
Source: ADAMO Clinical Study Report.[32]

Safety Results

Safety data are summarized in Table 16. A total of 227 patients received more than one dose of denosumab in the long-term group (N = 111) or in the crossover group (N = 116) during the open-label phase, constituting the safety analysis set for that phase.

During the open-label phase, patient incidences of overall adverse events were 63% in the long-term group and 52% in the crossover group. System organ classes with the highest patient incidences of adverse events were [redacted] and infections and infestations (21%, 20%). By preferred term, the most frequent adverse events (patient incidence 5% in either treatment group) were back pain (5.4% long-term, 2.6% crossover), arthralgia (6.3%, 4.3%), and nasopharyngitis (4.5%, 6.0%). Most of the adverse events in both groups were reported as mild or moderate in severity.

Patient incidences of serious adverse events were 8.1% in the long-term group and 4.3% in the crossover group. By preferred term, no serious adverse events were reported for more than one patient; the system organ class with the highest patient incidences of serious adverse events was infections and infestations: five of 111 patients (4.5%) in the long-term group and one of 116 patients (0.9%) in the crossover group. One death was reported during the open-label phase as endocarditis (long-term group).

There were no reports of hypocalcemia, osteonecrosis of the jaw (ONJ), fracture healing complications, or atypical femoral fractures during the open-label phase. Rates of adverse events potentially associated with hypersensitivity, infections, skin infections, cardiovascular disorders, eczema, and acute pancreatitis were low and did not appear to increase over time.

Malignancy adverse events were reported for one of 111 patients (0.9%) in the long-term group (gastric cancer plus metastases to the lung plus rectal neoplasm [benign]) and two of 116 patients (1.7%) in the crossover group (bladder cancer; and malignant lung neoplasm plus metastases to central nervous system).

Median serum phosphorus decreased in the crossover group of patients who transitioned from placebo to denosumab during the open-label phase. Median serum calcium at months 12 and 24 was similar to that at baseline for both the long-term and crossover groups. Denosumab administration was not associated with changes in other serum chemistry or hematology parameters or clinically significant changes in vital signs.

TABLE 16: SUMMARY OF SAFETY RESULTS

Number (%)	Double-Blind Period		Open-Label Period	
	Placebo 60 mg Q6M N = 120	Denosumab 60 mg Q6M N = 120	Placebo/ Denosumab 60 mg Q6M N = 116	Denosumab/ Denosumab 60 mg Q6M N = 111
Adverse events				
All	87 (72.8)	87 (72.5)	60 (51.7)	70 (6.31)
Serious	11 (9.2)	13 (10.8)	5 (4.3)	9 (8.1)
Leading to study discontinuation	0	4 (3.3)	0	1 (0.9)
Leading to drug discontinuation	0	5 (4.2)	0	0
Death	1 (0.8)	1 (0.8)	0	1 (0.9)
Death due to endocarditis	0	0	0	1 (0.9)
Death due to myocardial infarction	0	1 (0.8)	0	0
Death due to basilar artery thrombosis	1 (0.8)	0	0	0
Serious adverse events	11 (9.2)	13 (10.8)	5 (4.3)	9 (8.1)
Infections and infestations	1 (0.8)	0	1 (0.9)	5 (4.5)
Neoplasms	1 (0.8)	3 (2.5)	2 (1.7)	1 (0.9)
[redacted]				
[redacted]				
[redacted]				
Adverse events (reported > 3%)	87 (72.8)	87 (72.5)	60 (51.7)	70 (6.31)
Back pain	8 (6.7)	10 (8.3)		
Arthralgia	7 (5.8)	8 (6.7)		
Nasopharyngitis	9 (7.5)	8 (6.7)		
Osteoarthritis	2 (1.7)	5 (4.2)		
Hypertension	5 (4.2)	1 (0.8)		
Hypercholesterolemia	1 (0.8)	3 (2.5)		
Myalgia	5 (4.2)	2 (1.7)		
Fall	3 (2.5)	2 (1.7)		
Influenza	4 (3.3)	1 (0.8)		
Headache	5 (4.2)	1 (0.8)		
Diarrhea	4 (3.3)	2 (1.7)		
Constipation	7 (5.8)	0		

Q6M = single doses at the first and sixth months.
Source: ADAMO Clinical Study Report.[32]

Conclusion

ADAMO extension was a 12-month open-label period that enrolled 228 male patients with low BMD. Patients were treated with denosumab 60 mg Q6M. There were no new safety concerns with extended use of denosumab during the extension period. Patients who received denosumab during both study periods (double-blind and open-label) continued to have an increase in BMD during the 12-month open-label phase. Patients who transitioned from placebo in the double-blind phase to denosumab 60 mg Q6M in the open-label period experienced gains in BMD that were consistent with those experienced by patients who received denosumab during the double-blind phase.

APPENDIX 7: SUMMARY OF INDIRECT COMPARISONS

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Aim of the Supplemental Issue

The objective of this section is to summarize and critically appraise the indirect comparison (IDC) provided to the CADTH Common Drug Review (CDR) by the manufacturer for the purpose of this review.[9]

Summary of the Manufacturer's Indirect Comparison

Objectives

To compare denosumab with zoledronic acid when used to increase bone mineral density in men with osteoporosis.

Methods

[redacted]

Figure deleted as per the manufacturer's request.

[redacted]

Figure deleted as per the manufacturer's request.

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Results

[redacted]

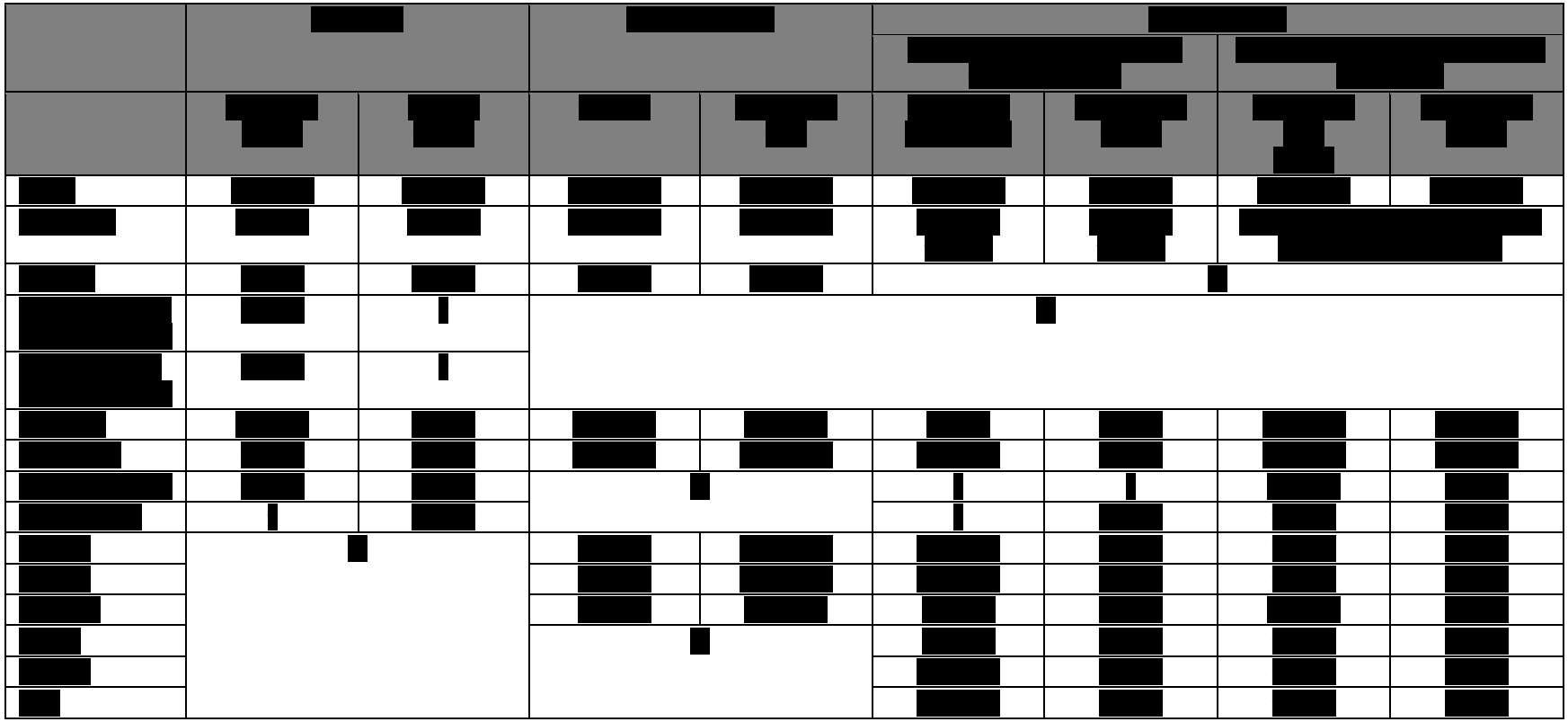
[redacted]

[redacted]

[redacted]	[redacted]			
	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	

[redacted]

[redacted]



[redacted]

Critical Appraisal and Discussion

The included studies had similar patient populations in terms of age and baseline osteoporosis severity. Acceding to a clinical expert consulted by CDR, the patient characteristics for the included studies reflect the profile of Canadian men with osteoporosis. Denosumab, zoledronic acid, and alendronate dosing strategies are in line with the Health Canada–approved labels for the products.

There were several limitations noted for the IDC report. The authors conducted two separate IDCs, but did not report the rationale for performing two rather than a single IDC. The second IDC included a study that was not included in the first IDC. From the information provided in the report, there were no obvious reasons for not including the Boonen study in the first IDC. Moreover, very little information was provided to allow for an assessment of methodological rigour concerning the conduct of the analytical portion of the network meta-analysis. Overall, there were few studies included in the IDCs. The small number of studies included and the correspondingly small number of included patients resulted in wide ranges in confidence intervals, which reflects a high degree of uncertainty regarding the results of the IDCs. While both IDCs compared denosumab versus zoledronic acid, the two IDCs provided inconsistent results in terms of lumbar spine BMD. As the authors did not provide guidance as to which IDC might be more reliable, and in light of the aforementioned limitations that are associated with a high degree of uncertainty, the true relative efficacy of denosumab compared with zoledronic acid is unclear. Nevertheless, the most parsimonious conclusion given the available data is that the results of the IDC suggest that there are no major differences between the efficacy of denosumab and zoledronic acid in treating osteoporosis in men.

The authors did not compare denosumab with all potentially relevant comparators, most notably other oral bisphosphonates such as alendronate and risedronate. However, the clinical expert suggested that such comparison is not necessary given that both denosumab and zoledronic acid are considered second-line therapies for osteoporosis, while oral bisphosphonates are considered to be first-line treatments due to the route of administration convenience and lower cost. Similarly, comparators such as teriparatide are not relevant given their status as third-line treatments reserved for patients for whom initial therapy is inappropriate. Therefore, in the context of current clinical practice, the absence of other comparators besides zoledronic acid is not a serious limitation.

CDR reviewers conducted an independent literature search for published IDCs that compared denosumab with other available drugs when used for the treatment of osteoporosis in men, but were unable to identify any published alternatives to IDC provided by the manufacturer.

Conclusions

The results of the two IDCs provided by the manufacturer of denosumab that compared denosumab with zoledronic acid were consistent in demonstrating that there are no statistically significant differences between the effects of denosumab and zoledronic acid on the change in BMD after 12 months in the hip, femoral neck, and trochanter. In one of the two IDCs, denosumab was associated with a small but statistically significantly greater improvement in BMD versus zoledronic acid only in the lumbar spine, but no such difference was detected in the other IDC. Therefore, there is no clear evidence of clinically relevant differences in the increase in BMD associated with denosumab and zoledronic acid treatment in men with osteoporosis. The biggest limitation with the aforementioned IDCs is the small number of trials that were included, and a correspondingly high degree of uncertainty associated with the results. Although potential harms were not analyzed in the IDC, the available evidence suggests that denosumab and zoledronic acid do not have markedly different safety profiles.

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