APPENDIX 3: SUMMARY OF STUDY CHARACTERISTICS OF INCLUDED STUDIES

Trial Design	Inclusion Criteria	Interventions and Comparators	Relevant Outcomes	Notes
DENOSUMAB				
FREEDOM International, multicentre, placebo-controlled, DB RCT Cummings 2009[18] Jamal 2011[36] N = 7,868 enrolled (number of patients who completed the study not reported)	Postmenopausal women with osteoporosis between 60 and 90 years with a T-score between -2.5 and -4 at lumbar spine or total hip. Use within 12 months or lifetime use > 3 years of bisphosphonates was not allowed. Patients with any severe fracture or > 2 moderate prevalent vertebral fractures were excluded.	**Denosumab** (n = 3,902) SC injection of 60 mg every 6 months **Placebo** (n = 3,906) SC injection every 6 months **Other medication:** Daily calcium (≥1000 mg) supplementation. Daily vitamin D (≥400 UI) supplementation if required. **Duration:** 36 months	**Primary efficacy:** New vertebral fractures (as assessed centrally using a semi-quantitative grading scale on annually-taken lateral spine radiographs). **Secondary efficacy:** Time to first non-vertebral and hip fractures, as well as BMD. **Harms:** AEs, SAEs, deaths, WDs, WDEAs.	Manufacturer-funded. Fractures of skull, face, mandible, metacarpals, fingers, or toes were excluded, as they are not associated with low BMD. Discontinuation from the study was required if total hip BMD ↓ by > 7% over 12 months or by ≥ 10% during the study, or if T-score was < –4.0.
ZOLEDRONIC ACID				
HORIZON PFT International, multicentre, placebo-controlled, DB RCT Black 2007[19] Secondary publications: Boonen 2008[37] Grbic 2008[29] Grbic 2010[30] Reid 2010[38] Black 2010[33]	Postmenopausal women with osteoporosis between 65 and 89 years with a T-score ≤ –2.5 at the femoral neck, or with a T-score ≤ –1.5 and at least 2 mild vertebral fractures or 1 moderate vertebral fracture. Previous use of bisphosphonates allowed with washout period, which was dependent on duration of previous use. Concomitant use of some osteoporosis medication allowed, including	**Zoledronic acid** (n = 3,889) 5 mg IV at baseline, 12 months and 24 months **Placebo** (n = 3,876) IV administration at baseline, 12 months and 24 months **Other medication:** Daily calcium (1,000-1,500 mg) and vitamin D (400-1,200 IU) supplementation. **Duration:** 36 months	**Primary efficacy:** New vertebral fractures in patients not taking osteoporosis medication at randomization (as assessed centrally using quantitative morphometry and standard methods on annually-taken lateral spine radiographs). Hip fractures in the whole patient population. **Secondary efficacy:** Non-vertebral fractures, clinical fractures, change in BMD.	Manufacturer-funded. Fractures of toe, facial bone, finger, and excessive trauma fractures excluded. Patients who took allowed medication were placed in strata 2 (n = 1,652), while patients in strata 1 did not take any osteoporosis medication (n = 6,113). Discontinuation from the

Trial Design	Inclusion Criteria	Interventions and Comparators	Relevant Outcomes	Notes
n = 18,421 screened N = 7,765 randomized N = 5,975 completed study (77%)	HRT, raloxifene, and calcitonin.		**Harms:** AEs, SAEs, deaths, WDs, WDEAs.	study was required if BMD ↓ by > 8% at year 1 or 10% at year 2.
RALOXIFENE				

MORE
International, multicentre, placebo-controlled, DB RCT
 	
Ettinger 1999[20]
Secondary publications:
Siris 2002[26]
Delmas 2002[25]
Maricic 2002[24]
Barrett-Connor 2002[39]
Qu 2005[40]
Oleksik 2005[28]
Melamed 2011[31]
 	
N = 22,379 screened
N = 7,705 randomized
N = 5,692 completed (74%)
	Postmenopausal women with osteoporosis with:
	• A T-score ≤ -2.5 at the femoral neck or lumbar spine, or
	• Low BMD plus:
	  ○ at least 1 moderate or severe vertebral fracture or
	  ○ at least 2 mild vertebral fractures, or
	• At least 2 moderate fractures regardless of BMD.
	
	Use of bisphosphonates within the previous 6 months was not allowed.
		Raloxifene 60 mg PO daily (n = 2557)
		Raloxifene 120 mg* PO daily (n = 2572)
		Placebo (n = 2576)
		
		Other medication:
		Daily calcium (500 mg) and vitamin D (400-600 IU) supplementation.
		
		Duration: 36 months
		(in addition to a 12-month extension period where bone-active medications were allowed)
			Efficacy:
			Incident vertebral fractures, as assessed centrally using a semi-quantitative scale on vertebral radiographs.
			Non-vertebral fractures, determined by direct questioning.
			BMD.
			
			Harms:
			AEs, SAEs, deaths.
				Manufacturer-funded.
				
				Fractures resulting from traffic collision, assault, falling, or moving object are considered traumatic and, hence, excluded.
				
				Discontinuation from the study was required if:
				• BMD ↓ ≥ 7% at lumbar spine or 10% at femoral neck at yr 1.
				• BMD ↓ ≥ 11% at lumbar spine or 14% at femoral neck (yr 2).
				• Patients experienced > 2 incident vertebral fractures.

CORE International, multicentre, placebo-controlled, DB RCT Siris 2005[5] N = 4,011 enrolled in	Postmenopausal women with osteoporosis who participated in the MORE study. <u>CORE BMD sub-study:</u> Patients from the U.S. sites who had a valid BMD measurement at year 3, who	<u>CORE BMD sub-study:</u> **Raloxifene 60 mg PO daily** (n = 259) **Placebo** (n = 127) **Other medication:** Daily calcium (500 mg) and vitamin D (400-600 IU)	<u>CORE BMD sub-study:</u> **Efficacy:** BMD (lumbar spine and femoral neck). **Harms:** Harms outcomes are not reported for this particular subset of the	Manufacturer-funded. CORE was the continuation from the MORE trial and was designed to assess the effects of raloxifene on breast cancer for four additional years beyond MORE. Focus will be given

Trial Design	Inclusion Criteria	Interventions and Comparators	Relevant Outcomes	Notes
CORE <u>BMD sub-study:</u> N = 844 enrolled N = 386 analyzed N completed not reported	were at least 80% compliant with study medication and who did not take any other bone-active agents.	supplementation. **Duration:** 48 months (BMD outcome was reported for 7 years, i.e. 48 months in MORE and 36 months in CORE)	population.	here to the CORE BMD sub-study.
Michalska Single-centre, placebo-controlled DB RCT with an open-label active-controlled arm Michalska 2006[22] N = 125 screened N = 100 enrolled N = 99 randomized N = 99 completed (100%)	Postmenopausal women with osteoporosis between 50 and 80 years treated with alendronate 10mg/day for >3 years with a T-score <-2.5 at the lumbar spine or proximal femur before initiation of alendronate. **All patients had previous bisphosphonate experience.** Use of medication that might influence bone turnover was not allowed.	**Raloxifene 60 mg PO daily** (n = 33) **DB Raloxifene Placebo** (n = 33) **O/L Alendronate 10 mg PO daily** (n = 33) **Other medication:** Daily calcium (500 mg) and vitamin D (800 IU) supplementation. **Duration:** 12 months	**Primary efficacy:** BMD (change from baseline in vertebral BMD after 12 months within and between groups). **Secondary efficacy:** BMD (change in total hip and femoral neck BMD between groups). **Harms:** AEs, WDEAs.	Not manufacturer-funded. Double-blind medication was provided by Eli Lilly. Michalska is the only trial included in this review with a population of post-menopausal women with osteoporosis being systematically treated with a bisphosphonate immediately prior to the start of the trial.
Silverman International, multicentre, placebo-controlled and active-controlled DB RCT Silverman 2008[23] Christiansen 2010[41] N = 26,749 screened N = 7,492 randomized N = 6,847 analyzed	Postmenopausal women with osteoporosis between 55 and 85 years with a T-score between -2.5 and -4 at lumbar spine or femoral neck, or with at least one mild radiographically-confirmed vertebral fracture. Use of bisphosphonates and other osteoporosis treatments was prohibited within six months of screening.	**Bazedoxifene[†] 20 mg PO daily** (n = 1886) **Bazedoxifene[†] 40 mg PO daily** (n = 1872) **Raloxifene 60 mg PO daily** (n = 1849) **Placebo** (n = 1885) **Other medication:** Daily supplementation with calcium (up to 1200 mg) and vitamin D (400-800 IU).	**Primary efficacy:** New vertebral fracture (incidence of radiographically-confirmed fractures after 36 months). **Secondary efficacy:** Clinical vertebral fractures. Non-vertebral fractures. BMD (change from baseline in lumbar spine, total hip and femoral neck). **Harms:**	Manufacturer-funded.

Trial Design	Inclusion Criteria	Interventions and Comparators	Relevant Outcomes	Notes
N = 4,991 completed (67%)		**Duration:** 36 months	AEs, SAEs, deaths, WDs, WDEAs.	

AE = adverse event; BMD = bone mineral density; DB = double-blind; HRT = hormone replacement therapy; IV = intravenous; O/L = open-label; PO = orally; RCT = randomized controlled trial; SAE = serious adverse event; WD = withdrawal; WDAE = withdrawal due to AE.

* Raloxifene 120 mg exceeds the recommended dosage in Canada.

† Bazedoxifene is not approved in Canada. For both, only the raloxifene 60 mg treatment groups are of interest to this review.