Supplement Appendixes

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* This supplemental material was provided by the authors to give readers further details on their article. The material was not copyedited.

Appendix 1. Evidence-to-Decision (EtD) Framework: Treatments to Prevent Fractures in Patients with Osteoporosis, Treatments vs. Placebo

Comparative Effectiveness of Treatments to Prevent Fractures in Patients with Osteoporosis vs. Placebo	
POPULATION:	Patients with Osteoporosis
INTERVENTION:	Bisphosphonates, RANK ligand inhibitor (denosumab), sclerostin inhibitor (romosozumab), sequential sclerostin inhibitor (romosozumab) to bisphosphonate (alendronate), PTHrP (abaloparatide), recombinant PTH (teriparatide), SERM (bazedoxifene, raloxifene)
COMMON COMPARATOR:	Placebo
MAIN OUTCOMES:	Fractures (hip, clinical vertebral, any clinical fracture, radiographic vertebral), serious adverse events, withdrawals due to adverse events, and other harms
SETTING:	Institutionalized settings or community

ASSESSMENT

Desirable and undesirable effects
How substantial are the desirable and undesirable anticipated effects for each intervention?

Judgement (females)

Research evidence (females)

Desirable Effects
Large: None

Medium:
- Bisphosphonates
- Denosumab

Small:
- Teriparatide
- Romosozumab to Alendronate
- Raloxifene

Trivial:
- Abaloparatide
- Romosozumab
- Bazedoxifene

Varies: None
Don't know: None

Undesirable Effects
Large: None
Medium: None

Small:
- Teriparatide

Trivial:
- Bisphosphonates
- Abaloparatide
- Denosumab
- Romosozumab

Table 1a. Summary of Findings (SoF), Interventions vs. placebo

Treatment	Relative Risk from Network Meta-analysis Certainty of Evidence Absolute Risk Difference of Events per 1,000 (provided only when direct pair-wise meta-analysis' relative estimate is available)					
	Fractures				Harms	
≥ 36 mo.	**Hip**	**Clinical Vertebral**	**Any Clinical fracture**	**Radiographic Vertebral**	**Serious AEs***	**Withdrawal due to AEs**
Bisphosphonates	0.64 (0.50,0.82) ⊕⊕⊕ 6 fewer (11 fewer to 1 fewer)	0.38 (0.24,0.62) ⊕⊕⊕ 18 fewer (26 fewer to 13 fewer)	0.79 (0.68,0.91) ⊕⊕⊕ 24 fewer (42 fewer to 7 fewer)	0.49 (0.40,0.61) ⊕⊕⊕ 56 fewer (84 fewer to 33 fewer)	1.00 (0.89,1.11) ⊕⊕⊕ 2 fewer (34 fewer to 31 more)	0.94 (0.86,1.03) ⊕⊕⊕ 0 fewer (20 fewer to 5 more)
PTHrP (abaloparatide)	---	---	---	---	---	---
Recombinant PTH (teriparatide)	---	---	---	---	0.77 (0.48,1.22) ⊕◯◯ 36 fewer (91 fewer to 20 more)	2.93 (1.79,4.80) ⊕⊕◯ 127 more (73 more to 181 more)
RANK ligand inhibitor (denosumab)	0.61 (0.37,0.98) ⊕⊕◯ 4 fewer (8 fewer to 0 fewer)	0.32 (0.21,0.48) ‡ ⊕⊕⊕ 16 fewer (22 fewer to 11 fewer)	0.81 (0.69,0.96) ‡ ⊕⊕◯ 14 fewer (25 fewer to 3 fewer)	0.32 (0.20,0.54) ⊕⊕◯ 48 fewer (58 fewer to 39 fewer)	1.03 (0.83,1.27) ⊕⊕◯ 8 more (12 fewer to 27 more)	1.15 (0.85,1.54) ⊕⊕◯ 3 more (4 fewer to 10 more)
Sclerostin inhibitor (romosozumab)	---	---	---	---	---	---
Sequential Sclerostin inhibitor (romosozumab) to	---	---	---	---	---	---
SERM (bazedoxifene)#	0.93 (0.47,1.81) ⊕◯◯ 1 fewer	0.68 (0.29,1.60) ⊕⊕◯ 2 fewer (6 fewer to 3 more)	0.88 (0.64,1.22) ⊕◯◯ 6 fewer (18 fewer to 6 more) †	0.59 (0.43,0.79) ‡ ⊕⊕◯ 17 fewer (27 fewer to 7 fewer)	1.07 (0.85,1.34) ⊕⊕◯ 12 more (9 fewer to 34 more)	1.14 (1.01,1.30) ⊕⊕◯ 16 more (3 fewer to 35 more) §

- Romosozumab to Alendronate
- Bazedoxifene
- Raloxifene

Varies: None

Don't know: None

	(5 fewer to 4 more)					
SERM (raloxifene)	1.12 (0.64,1.94) ⊕◯◯ 1 more (3 fewer to 5 more)	0.69 (0.38,1.27) ⊕⊕◯ 8 fewer (29 fewer to 12 more)	0.92 (0.72,1.16) ⊕⊕◯ 6 fewer (18 fewer to 6 more) †	0.59 (0.48,0.71) ‡ ⊕⊕◯ 28 fewer (57 fewer to 1 fewer)	0.99 (0.78,1.26) ⊕⊕◯ 1 fewer (26 fewer to 24 more)	1.14 (1.02,1.27) ⊕⊕⊕ 15 more (1 more to 28 more)
12 to <36 mo.	**Hip**	**Clinical Vertebral**	**Any Clinical fracture**	**Radiographic Vertebral**	**Serious AEs***	**Withdrawal due to AEs**
Bisphosphonates	0.65 (0.43,0.97) ⊕⊕◯ 8 fewer (22 fewer to 2 more) §	0.46 (0.24,0.89) ⊕⊕⊕ 21 fewer (46 fewer to 4 fewer)	0.68 (0.51,0.92) ⊕⊕⊕ 59 fewer (106 fewer to 12 more)	0.44 (0.36,0.53) ⊕⊕◯ 44 fewer (65 fewer to 27 fewer) §	1.02 (0.85,1.22) ⊕⊕◯ 12 more (47 fewer to 91 more)	1.01 (0.72,1.40) ⊕◯◯ 3 more (10 fewer to 19 more)
PTHrP (abaloparatide)	---	---	0.24 (0.11,0.53) ⊕⊕◯ 29 fewer (45 fewer to 14 fewer)	0.14 (0.05,0.38) ⊕⊕◯ 36 fewer (52 to 21 fewer)	0.89 (0.67,1.18) ‡ ⊕⊕◯ 12 fewer (42 fewer to 17 more)	1.76 (1.30,2.39) ⊕◯◯ 38 more (11 more to 64 more)
Recombinant PTH (Teriparatide)	0.50 (0.12,1.98) ⊕◯◯ 4 fewer (12 fewer to 4 more)	0.24 (0.08,0.71) ⊕◯◯ 45 fewer (76 fewer to 15 fewer)	0.44 (0.31,0.62) ⊕⊕⊕ 27 fewer (56 fewer to 7 fewer)	0.19 (0.14,0.26) ⊕⊕⊕ 69 fewer (112 fewer to 28 fewer)	0.91 (0.69,1.21) ‡ ⊕⊕◯ 10 fewer (39 fewer to 20 more)	1.32 (1.03,1.69) ⊕⊕◯ 17 more (8 fewer to 42 more) §
RANK ligand inhibitor (denosumab)	---	0.83 (0.07,9.64) ◯◯◯ --	1.00 (0.48,2.09) ⊕◯◯ 1 fewer (27 fewer to 24 more)	0.27 (0.14,0.52) ⊕⊕◯ 64 fewer (92 fewer to 36 fewer)	0.98 (0.66,1.46) ⊕⊕◯ 2 fewer (46 fewer to 42 more)	2.53 (0.49,12.98) ◯◯◯ 6 more (4 fewer to 17 more)
Sclerostin inhibitor (romosozumab)	---	0.18 (0.05,0.62) ⊕⊕◯ 4 fewer (6 fewer to 1 fewer)	0.64 (0.47,0.89) ‡ ⊕⊕◯ 9 fewer (15 fewer to 2 fewer)	0.27 (0.16,0.47) ⊕⊕◯ 13 fewer (18 fewer to 8 fewer)	1.10 (0.95,1.27) ‡ ⊕⊕◯ 9 more (5 fewer to 22 more)	0.88 (0.59,1.31) ⊕◯◯ 2 fewer (7 fewer to 4 more)
Sequential Sclerostin inhibitor (romosozumab) to bisphosphonate (alendronate)	0.40 (0.23,0.70) ⊕⊕◯ --	0.19 (0.08,0.46) ⊕⊕◯ --	0.51 (0.29,0.89) ⊕◯◯ --	0.22 (0.16,0.31) ⊕⊕◯ --	0.97 (0.71,1.33) ⊕⊕◯ --	0.90 (0.61,1.35) ⊕◯◯ --
SERM (bazedoxifene)	---	---	---	---	---	---

SERM (raloxifene)	---	0.05 (0.00,0.81) ⊕◯◯ 35 fewer (62 fewer to 8 fewer)	0.11 (0.02,0.54) ⊕⊕◯ 53 fewer (88 fewer to 19 fewer)	0.26 (0.02,2.82) ◯◯◯ 15 fewer (45 fewer to 15 more)	0.59 (0.22,1.63) ◯◯◯ 29 fewer (88 fewer to 30 more)	2.59 (0.77,8.74) ◯◯◯ 49 more (3 fewer to 101 more)

Color key: Favors treatment; Favors comparator; No difference.
GRADE certainty of evidence (CoE): No evidence ---; Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕
*The FDA Code of Federal Regulations defines serious adverse effects as any event or reaction that results in death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect (FDA Code of Federal Regulations Title 21 (21CFR) 312.32 [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32, MedDRA (former COSTART) coding system
‡Direct comparison estimate (NMA data reported by default). The CGC reviewed the results from both the direct evidence and NMA, using the highest certainty of evidence that was available.
§Inconsistent confidence interval between relative and absolute effect, due to differences in network estimates and direct-pairwise estimates, which are used to calculate the absolute estimates
Available in the US as a combined formulation of conjugated estrogens/bazedoxifene FDA warning: There is an increased risk of endometrial cancer in a female with a uterus who uses unopposed estrogens; The Women's Health Initiative (WHI) estrogen-alone sub study reported increased risks of stroke and deep vein thrombosis; The WHI Memory Study estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal females 65 years of age and older

Additional Benefits
Quality of Life and Functional Outcomes

Only 1 eligible RCT reported on quality of life. The AAC trial narratively reported that alendronate was superior to placebo for "exercise gymnastic score" at 24 months (1). The other RCT found significant improved on the Oswestry Disability Index with 36 months of zoledronate versus placebo (2).

Additional Harms

Table1b.i. Adverse effects of treatments for osteoporosis in randomized trials and observational studies

Comparison	**Atypical Femoral Fractures** **Number of Studies Sample Size** **Time of outcome assessment**	**Osteonecrosis of the Jaw** **Number of Studies Sample Size** **Time of outcome assessment**	**Atrial Fibrillation** **Number of Studies Sample Size** **Time of outcome assessment**
Placebo or Unexposed Comparisons			
Bisphosphonates vs. placebo or unexposed	4 RCTs (2-5) (N = 15,014) RCTs 24-36 months. 13 observational studies (6-14); 4 studies in 2 publications (13, 14) (N = 4,549,171) observational: 3-10 years (if reported)	5 RCTs (2-5, 15) (N = 11,743) RCTs 24-36 months. 8 observational studies (16-23) (N = 1,354,375) observational: 2-8 years (if reported) Meta-analysis of 1 RCT at 12 months; N = 7,157 RR, 3.00; 95% CI, 0.12,73.51	5 RCTs (4, 5, 15, 24, 25) (N = 10,649) RCTs 24-36 months. 7 observational studies (N = 302,387) (26-32) observational: 12 to 60 months (if reported)

	Meta-analysis of 2 RCTs; N = 14,195 RR, 1.33; 95% CI, 0.21,7.66 2 RCTs had zero events Meta-analysis of observational studies was not possible due to clinical and statistical heterogeneity ⊕◯◯	Meta-analysis of 1 RCT at 36 months; N = 7,714 RR, 1.00; 95% CI, 0.06,15.94 4 RCTs had zero events Meta-analysis of 5 observational studies; N = 864,321 aRR, 3.37; 95% CI, 1.91,5.24 ⊕◯◯	Meta-analysis of 3 RCTs at 24 months; N = 2,452 RR, 1.00; 95% CI, 0.50,1.81 Meta-analysis of 1 RCT at 36 months; N = 7,714 RR, 1.28; 95% CI, 0.95,1.74 Meta-analysis of 6 observational studies; N = 284,780 aRR, 0.99; 95% CI, 0.77,1.30 ⊕◯◯
Denosumab vs. placebo	2 RCTs (33, 34); N = 8,718 RCTs 24-36 months Both RCTs experienced zero events at 36 months. In a 7-year extension of FREEDOM, only 2 AFFs were observed. Not rated	2 RCTs (33, 34); N = 8,718 RCTs 24-36 months Not rated	1 RCT (34); N = 7,714 RCT 36 months Meta-analysis of 1 RCT; N = 7,714 RR, 1.00; 95% CI, 0.60,1.67 ⊕◯◯
Romosozumab vs. placebo	1 RCT (35); N = 7,157 RCT 12 months Meta-analysis of 1 RCT; N = 7,157 RR, 3.00 (95% CI, 0.12,73.51) ◯◯◯	1 RCT (35); N = 3,581 RCT 12 months Meta-analysis of 1 RCT; N = 3,581 RR 3.00 (0.12,73.51) ◯◯◯	No data
Raloxifene, calcitonin, or teriparatide, denosumab, or estrogens vs. unexposed	Raloxifene, calcitonin, or teriparatide vs. unexposed: 1 observational study (9) N = 8,853 Observational 40 months (average) Meta-analysis of 1 observational study; N = 8,853 aRR, 0.49 (0.22,1.12) ◯◯◯	No data	Raloxifene, calcitonin, teriparatide, denosumab, or estrogens vs. unexposed: 1 observational study (29); N = 136,982 observational NR Meta-analysis of 1 observational study; N = 136,982 aRR, 1.13 (95% CI, 0.91,1.42) ◯◯◯
Head-to-Head Comparisons			
Romosozumab then alendronate vs. alendronate	1 RCT (36); N = 4,054 RCT 24 months Meta-analysis of 1 RCT; N = 4,054 RR, 0.49 (95% CI, 0.09,2.69) ◯◯◯	1 RCT (36); N = 4,054 RCT 24 months Meta-analysis of 1 RCT; N = 7,180 RR, 0.99; 95% CI, 0.06,15.77) ◯◯◯	No data

Denosumab vs. zoledronate	1 RCT (37); N = 57 RCT 24 months 1 RCT observed zero AFF Not rated	1 RCT (37); N = 57 RCT 24 months Not rated	No data
Bisphosphonates vs. raloxifene	1 observational study (38) N = 324,397 1,094,049 vs. 158,722 patient-years of continuous exposure Meta-analysis of 1 observational study; N = 324,397 aRR, 1.51; 95% CI, 1.23,1.84 ◯◯◯	3 observational studies (38-40); N = 342,842 observational 12 to 48 months (if reported) Meta-analysis of 2 observational studies; N = 332,944 aRR, 1.94; 95% CI, 0.75,12.42 ◯◯◯	2 observational studies (41, 42); N = 36,866 observational 10 to 12 months average Meta-analysis of 2 observational studies; N = 36,866 aRR, 0.83; 95% CI, 0.40,1.59 ◯◯◯
Bisphosphonates vs. raloxifene or calcitonin	1 observational study (43) N = 33,815 observational mean 2.13 years (SD 2.21) Meta-analysis of 1 observational study; N = 33,815 aRR, 1.03 (95% CI, 0.70,1.52) ◯◯◯	No data	No data
Bisphosphonates vs. raloxifene, calcitonin, or teriparatide	1 observational study (9) N = 5,119 observational 40 months (average) Meta-analysis of 1 observational study; N = 5,119 aRR, 0.63 (95% CI, 0.27,1.42) ◯◯◯	No data	No data
Bisphosphonate vs. denosumab	No data	No data	1 observational study (44); N = 32,470 observational NR Meta-analysis of 1 observational study; N = 32,470 aRR, 1.38; 95% CI, 1.03,1.85 ◯◯◯
Bisphosphonates vs. raloxifene or supplements (calcitonin, vitamin D, or ipriflavone)	No data	No data	1 observational study (45); N = 130,182

			observational Median 4 years Meta-analysis of 1 observational study; N = 130,182 aRR, 0.52 (95% CI, 0.29, 0.91) ◯◯◯

Included studies reported higher risk of some specific adverse events including nausea and hypercalcemia after treatment with peptide hormones when compared to both, placebo, and bisphosphonate. The risk of hot flashes or deep vein thrombosis is higher after treatment with SERMs when compared with placebo, although such specific harms were rare. aRR, adjusted relative risk

Table 1.b. ii. Pharmacovigilance reports for denosumab and anabolic drugs http://openvigil.sourceforge.net/

	Denosumab	**Romosozumab**	**Teriparatide**	**Abaloparatide**
Number of matching records	160,234	3,792	104,397	10,002
Gender distribution	123,205 (76.89%) females	2,882 (76%) females	93,781 (89.83%) females	9,385 (93.83%) females
	22,699 (14.17%) males	285 (7.52%) males	9,363 (8.97%) males	164 (1.64%) males
	665 (0.42%) unknowns		33 (0.03%) unknowns	
Age distribution	70 (3633)	78 (84)	75 (2590)	64 (236)
	74 (3291)	82 (74)	77 (1904)	63 (220)
	73 (3256)	79 (73)	76 (1898)	60 (202)
	68 (3196)	83 (71)	79 (1858)	61 (197)
Top adverse events Event (number of reports)	death (17,521)	fall (308)	nausea (8,596)	headache (,1582)
	arthralgia (7,028)	injection site pain (196)	arthralgia (8,266)	nausea (1,281)
	osteonecrosis of jaw (6,926)	arthralgia (130)	pain in extremity (8,112) dizziness (7,902)	dizziness (1,050)

Table 1.b.iii. Serious adverse events after anabolic drugs or denosumab indicated for the treatment of osteoporosis (Epocrates)

	Denosumab	**Romosozumab**	**Abaloparatide**	**Teriparatide**
anaphylaxis/angioedema	x	x	x	
calciphylaxis				x
cardiovascular death risk		x		
depression				x
drug reaction with eosinophilia and systemic syndrome	x			

erythema multiforme		x		
femur fractures, atypical	x	x		
hypercalcemia			x	
hypercalciuria			x	
hypocalcemia	x	x		
hypotension, orthostatic			x	x
infection, serious	x			
malignancy	x			
Risk of myocardial infraction		x		
multiple vertebral fractures (upon treatment discontinuation)	x			
musculoskeletal pain, severe	x			
osteonecrosis, jaw	x	x		
osteosarcoma			x	x
pancreatitis	x			
pneumonia				x
stroke		x		
vasculitis	x			

Judgement (males)	Research evidence (males)
Desirable Effects ○ Trivial ● **Small** ○ Medium ○ Large ○ Varies ○ Don't know **Undesirable Effects** ○ Large ○ Medium ○ Small ● **Trivial** ○ Varies ○ Don't know	**Evidence on Treatments in Male Adults** **Table 1c. Summary of Findings (SoF), Males with Osteoporosis**

	Hip	Clinical Vertebral	Any Clinical	Radiographic Vertebral	Nonvertebral	Serious Adverse Events	Withdrawals due to Adverse Events	Atrial Fibrillation
≥ 36 months								
Bisphosphonates 1 trial of alendronate **(46)** 134 participants	No data	No data	0.73 (0.27 to 1.98) 30 fewer (140 fewer to 70 more) ◯◯◯	0.42 (0.19 to 0.97) 140 fewer (266 fewer to 13 fewer) ⊕◯◯	0.73 (0.27 to 1.98) 30 fewer (140 fewer to 70 more) N/A	No data	No data	No data
12 to < 36 months								
Bisphosphonates **(5, 47-50)** 3 trials of zoledronate(5, 47, 48), 1 of risedronate (49), 1 trial of alendronate (50)	No data	0.35 (0.04 to 3.32) 3 fewer (10 fewer to 3 more) ◯◯◯	0.75 (0.43 to 1.25) 10 fewer (30 fewer to 10 more) ⊕⊕◯	0.39 (0.22 to 0.83) 18 fewer (62 fewer to 15 more) ⊕⊕◯	0.71 (0.28 to 1.79) 5 fewer (25 fewer to 12 more) N/A	0.95 (0.82,1.09) 12 fewer (55 fewer to 24 more) ⊕⊕⊕	0.66 (0.26,1.64) 2 fewer (70 fewer to 19 more) ⊕⊕◯	Meta-analysis of 2 RCTs; N = 1,988 1.06 (0.39,2.28) 2 more (14 fewer to 13 more) Adjusted meta-analysis of 1 observational study 1.53 (0.96,2.45) ⊕◯◯

Color key: Favors treatment; Favors comparator; No difference.

GRADE certainty of evidence (CoE): No evidence ---; Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕

Certainty of evidence What is the overall certainty of the evidence of effects for each intervention?		
Judgement (females)	**Research evidence (females)**	**Additional considerations**
High: • Bisphosphonates **Moderate:** • Abaloparatide • Denosumab • Romosozumab • Romosozumab to Alendronate **Low:** • Bazedoxifene • Teriparatide • Raloxifene **Insufficient:** None **No included studies:** None	See SoF table under "Desirable and Undesirable Effects."	N/A
Judgement (males)	**Research evidence (males)**	**Additional considerations**
What is the overall certainty of the evidence of effects? ○ Insufficient ●**Low** ○ Moderate ○ High ○ No included studies	See evidence under "Desirable and Undesirable Effects."	N/A

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
Judgement	**Research evidence**	**Additional considerations**
Important uncertainty or variability: None **Possibly important uncertainty or variability:** • Bisphosphonates, • Abaloparatide • Teriparatide • Denosumab, • Romosozumab, • Romosozumab to Alendronate • Bazedoxifene • Raloxifene **Probably no important uncertainty or variability:** None **No important uncertainty or variability:** None	Evidence on values and preferences (51-53) showed that females considered the effectiveness and adverse effects of treatments equally, followed by convenience of taking medication, and impact on daily routine (i.e., preferred less frequent dosing , oral route of administration, and injectable route over oral if take at a lower frequency)(51). Out-of-pocket costs were considered factors of extreme importance(51). Bisphosphonates can be taken through a variety of routes and frequencies, giving patients an opportunity to tailor treatment to their preferences (Table 2). Denosumab is only available by subcutaneous injection to be given every 6 months. Feedback from the CGC Public Panel reported preferences for the use of bisphosphonates to treat osteoporosis. Similar to the research evidence, the Public Panel's preferences were also driven by the benefits and harms profile. Five out of 8 members of from the Public Panel provided feedback on their preferences based on the findings from the systematic review informing the guideline; 5 of 8 members responded. • All of respondents indicated that they would take/recommend one or more of the medications presented to treat *osteoporosis*. • When asked what medications they would take/recommend to treat *osteoporosis*, only 3 respondents identified specific medications (N = 3/5) when presented with information about medications vs. placebo: o Preferences for bisphosphonates were identified by all respondents (n = 3/3) o Preferences for treatment with RANK ligand inhibitors (n = 2/3) & sclerostin inhibitors (n = 2/3) were identified o Preferences for sequential treatment (n = 2/3) and SERMs (n = 1/3) were also identified • All respondents indicated that they would take/recommend Bisphosphonates (Zoledronic acid) to treat *low bone mass* • Preferences for taking/recommending medications (overall) were primarily on balance of benefits vs. harms; other considerations that may have expected (e.g., costs, administration) were not cited, however panel members had this information within the survey or in supplemental document which was new from previous surveys	Critical outcomes evaluated included patient-oriented clinical outcomes of bone fractures, patient functional status, quality of life, and serious adverse events, and important outcomes included withdrawals due to adverse events. When evaluating the net benefits of the various treatments, we looked at rates of bone fractures at longer (≥36 months) and shorter time of outcome assessment (12 to < 36 months)(54). The CGC prioritized benefits and harms lasted ≥36 months, and cost-effectiveness from all oral and injectable medications regardless of treatment duration(51). Each study contributed to outcomes at one time point of fracture assessment (at 12 to < 36 months or ≥36 months). In addition, we prioritized the prevention of hip fractures and clinical vertebral fractures followed by the prevention of any clinical or radiographic vertebral fractures based on the high risk of disability, institutionalization, morbidity, and mortality in people with clinical fractures(55, 56) and the high risk of future fractures in people with radiographic fractures (57). Appendix Table 1 presents definitions of each fracture category. We also prioritized serious adverse events reported in randomized controlled trials (RCTs) and observational studies as more clinically important than withdrawals due to

		adverse events usually available from RCTs only. Overall, we contextualized the balance between benefits and harms based on the direction and the magnitude of treatment effects across all outcomes and considering the certainty of evidence. Informed decision-making about treatments for osteoporosis should be based on discussions with patients about potential benefits, harms, patient values and preferences about oral or injectable drug formulations, and costs.

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison for each intervention?		
Judgement (females)	**Research evidence (females)**	**Additional considerations**
Favors the intervention: • Bisphosphonates • Denosumab **Probably favors the intervention:** • Romosozumab to Alendronate • Raloxifene • Teriparatide **Does not favor either the intervention or the comparison:** • Abaloparatide • Romosozumab • Bazedoxifene **Probably favors the comparison:** None **Favors the comparison:** None **Varies:** None **Don't know:** None	See SoF table under "Desirable and Undesirable Effects."	
Judgement (males)	**Research evidence (males)**	**Additional considerations**
Does the balance between desirable and undesirable effects favor the intervention or the comparison? ○ Favors the intervention ○ Probably favor savors intervention	See evidence under "Desirable and Undesirable Effects."	

○ Does not favor either the intervention or the comparison ○ Probably favors the comparison ○ Favors the comparison ○ Varies ● **Don't know**		

Resources required
How large are the resource requirements (costs) for each intervention?

Judgement	Research evidence	Additional considerations
Large costs: • Teriparatide • Denosumab **Modest costs:** • Abaloparatide • Romosozumab • Romosozumab to Alendronate • Raloxifene **Negligible costs and savings:** • Bisphosphonates **Modest savings:** None **Large savings:** None **Varies:** None **Don't know:** Bazedoxifene	• Alendronate federal payment ceiling is the lowest when compared with ibandronate or risedronate (Table 1c). Brand formulations of bisphosphonates is much more expensive than available generic versions of the same drug (Table 1d). • There is a substantial variability in pharmacy prices for bisphosphonates with alendronate being the least and zoledronic acid being the most expensive medications (Table 1d). • The overall treatment cost is higher for injectable formulations that include reimbursement for clinic visits and potential missing work hours for working patients. • Annual cost per Medicare beneficiary is lower for generic than brand formulations (Figure 1a). • Bisphosphonates (Figure 1b) are much less expensive than other drug classes (Figure 1c). • Teriparatide is the most expensive followed by denosumab, abaloparatide, romosozumab, and raloxifene (Figure 1b). • Eligible RCTs reported on fracture outcomes after treatment with alendronate, risedronate, or zoledronate. The evidence on ibandronate, was limited to intermediate outcomes(51). • Prescribing medications without the evidence of their effects on fracture presents additional potentially unnecessary cost of care that should be justified. • **Table 1d. Federal Upper Limit as the Federal Payment Ceiling for Anti-osteoporosis Medications with ≥3 Generic Versions, 2021** Drug / Dose / Weighted Average Manufacturer Prices - Federal Upper Limit Alendronate sodium / 35mg / $18-31 Alendronate sodium / 70mg / $10-20 Ibandronate sodium / 150mg / $165-367 Risedronate sodium / 35 mg / $337-1861	

Risedronate sodium	150mg	$820-1958

Source: https://www.medicaid.gov/medicaid/prescription-drugs/federal-upper-limit/index.html, Accessed in July 2021

Table 1e. Pharmacy Cost for Brand or Generic Versions of Anti-osteoporosis Medications, 2021

Generic or Brand	Dose	Cost
alendronate sodium		
Generic	oral tablet, 5 mg (30 ea.)	$12.29
Generic	oral tablet, 10 mg (30 ea.)	$31.50
Generic	oral tablet, 40 mg (30 ea.)	$295.99
Generic	oral tablet, weekly: 35 mg (3 dose pack, 4 tabs)	$249.63
Generic	oral tablet, weekly: 70 mg (3 dose pack, 4 tabs)	$128.99
Brand	oral tablet, 70 mg (1 dose pack, 4 tabs)	$368.55
Brand	oral tablet, 70 mg (1 dose pack, 4 tabs)	$163.41
ibandronate sodium		
Generic	oral tablet, monthly: 150 mg (1 dose pack, 3 tabs)	$20.88
Brand	oral tablet, monthly: 150 mg (1 dose pack, 3 tabs)	$725.99
risedronate sodium		
Generic	oral tablet, weekly: 35 mg (1 dose pack, 4 tabs)	$239.99
Generic	oral tablet, 150 mg (1 dose pack, 1 tab)	$167.99
Brand	oral tablet, weekly: 35 mg (1 dose pack, 4 tabs)	$454.99
Brand	oral tablet, weekly: 35 mg (1 dose pack, 4 tabs)	$284.19
Brand	oral tablet: 150 mg (1 dose pack, 1 tab)	$421.99
zoledronic acid		
Generic	1 vial 4 mg base/100ml	$41.00 – $45.68
Brand	1 vial 5 mg base/100ml	$1,139.52
Brand	1 vial 4 mg base/5ml	$812.02
Brand	1 vial 4 mg base/100ml	$972.57

Source: http://www.goodrx.com; https://www.drugs.com/price-guide

Figure 1a. Medicare Part D Average Spending Per Dosage Unit for Brand or Generic Versions of Anti-osteoporosis Medications, 2019

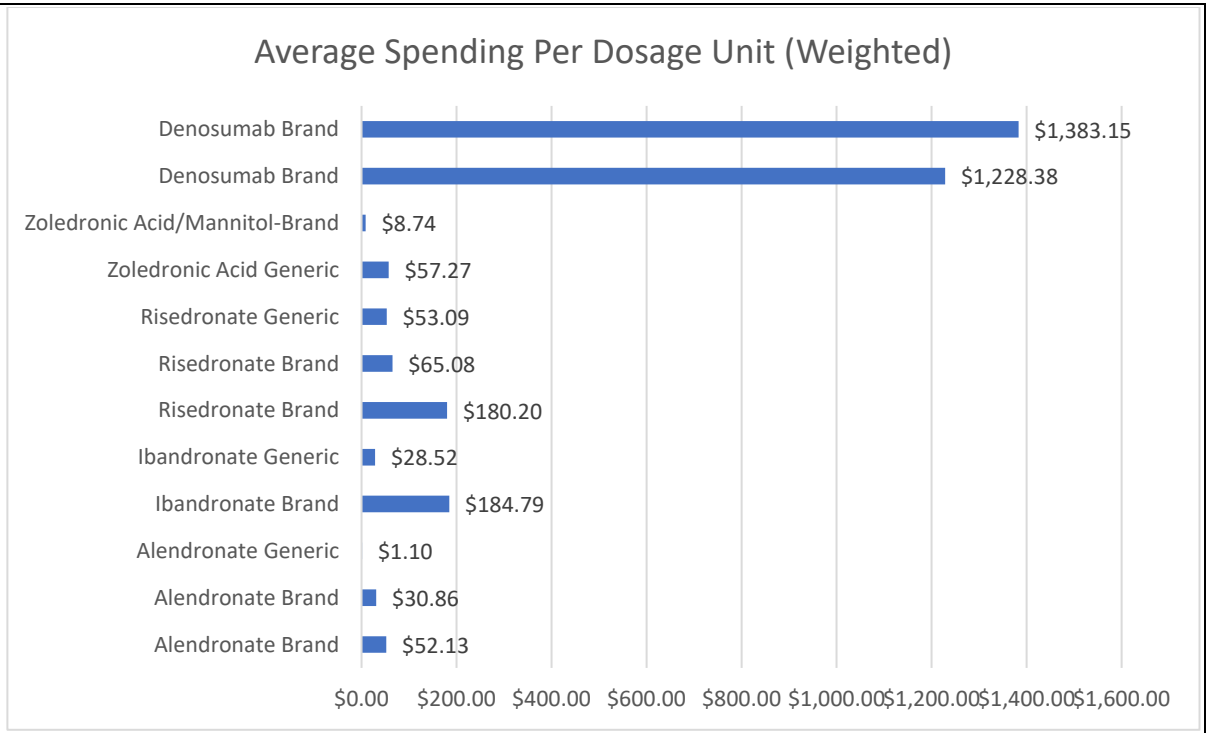


Figure 1b. Bisphosphonates

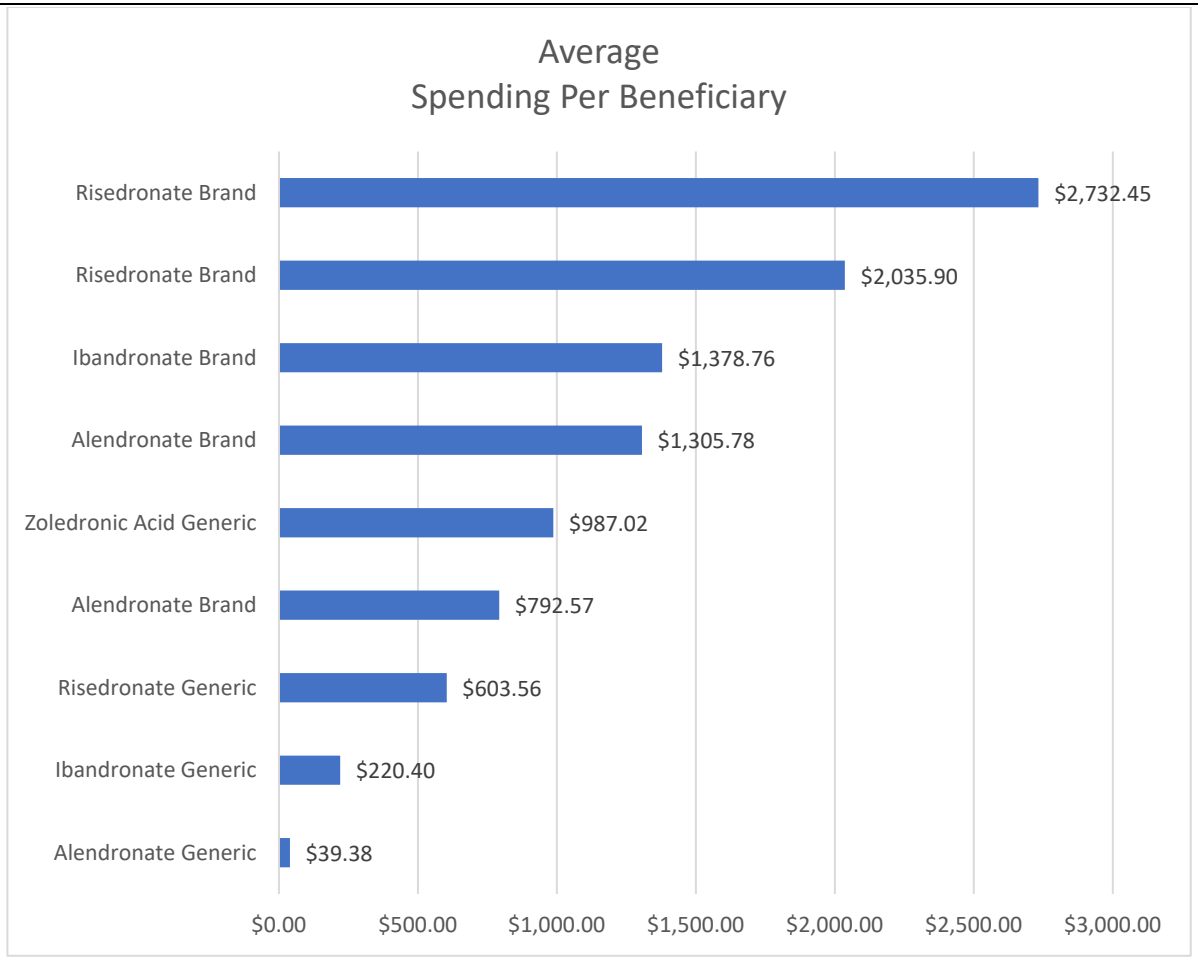
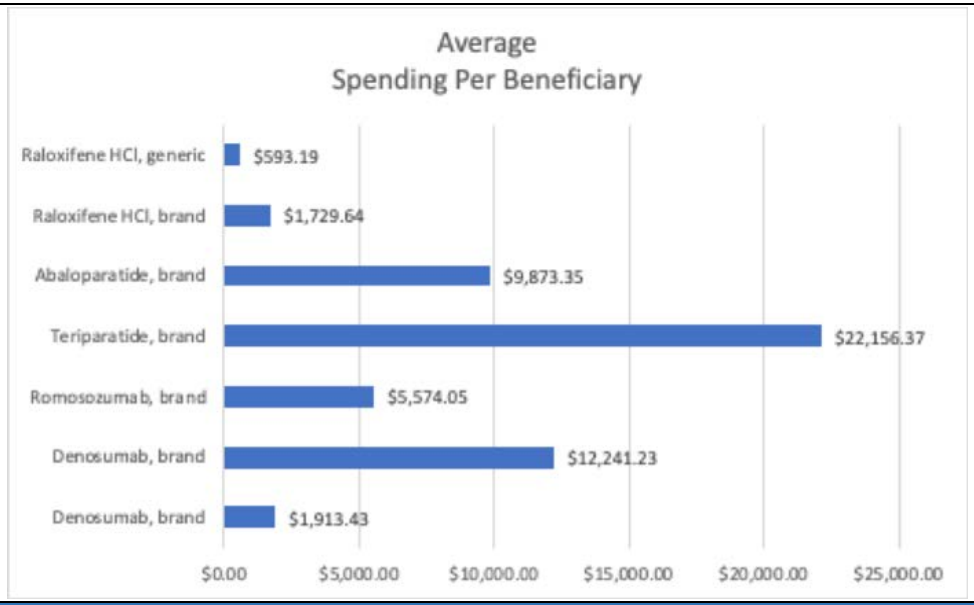


Figure 1c. Newer drugs



Cost effectiveness
Which intervention does the cost effectiveness favor?

Judgement	Research evidence	Additional considerations
Favors the comparison: None **Probably favors the comparison:** None **Does not favor either the intervention or the comparison:** None **Probably favors the intervention:** • Bisphosphonates **Favors the intervention:** None **Varies:** • Abaloparatide • Teriparatide • Denosumab • Romosozumab	We considered the national data on resource utilization and published systematic reviews of economic analyses of life-time horizon cost applicable to the US(58). National Medicare data suggested that bisphosphonates are substantially less expensive than the other drug classes (average annual spending per Medicare beneficiary among bisphosphonates ranged from $39 to $2,732 versus $593 to $22,156 among other medications (denosumab, SERM [raloxifene], PTHrP [abaloparatide], recombinant PTH [teriparatide], sclerostin inhibitor [romosozumab]; Appendix 1 Table 1d, Figures 1b and 1c)(59). The Medicare data also showed that generic oral alendronate or generic intravenous zoledronate were the least expensive when compared with brand formulations (Appendix 1 Table 1e). The overall treatment cost was probably higher for injectable intravenous formulations because the overall cost included reimbursement for clinic visits, infusion costs (intravenous), and potential missed work hours for working patients. A systematic review of 43 RCTs in 71,809 postmenopausal females concluded that the most cost-effective initial therapy of post-menopausal osteoporosis was generic zoledronate (cost per 1 hip fracture reduction=$7,995) or oral alendronate (cost per 1 hip fracture reduction=$19,488) (Appendix 1 Table 1f) (51, 60). This analysis did not address additional costs associated with injectable drugs or with brand formulations. Another systematic review (61) concluded that oral alendronate and risedronate had the maximum net benefit for patients with high baseline risk of fractures while gains in quality-adjusted life-years (QALYs) would be much smaller in patients with low baseline risk of fracture (Appendix 1 Table 1g). The authors concluded that intravenous bisphosphonates have much higher incremental cost-effectiveness ratios (> £50,000 per QALY) than no treatment and therefore do	

- Romosozumab to Alendronate
- Bazedoxifene
- Raloxifene

No included studies:
None

not meet thresholds for high value interventions in the UK(51).(51). The absolute cost to use denosumab, romosozumab, or teriparatide would be higher if discontinuation is followed with an alternative sequential treatment.

The evidence from the published CEAs was insufficient to conclude economic value of drugs for osteoporosis(51). The most recent systematic review of cost-effectiveness analyses of drug for osteoporosis included 12 CEAs but only one CEA was from the US (62). The review concluded that denosumab, zoledronic acid and teriparatide were cost-effective based on willingness to pay thresholds from countries where economic evaluations have been conducted(63)The review suggested that baseline risk of fracture, the magnitude of medication effects on fracture prevention, medication adherence and persistence, and drug cost contributed to cost-effectiveness of available medications(63). A single cost-effectiveness analysis conducted in the US (62) concluded that denosumab was cost-effective compared to other osteoporotic treatments in older osteoporotic US males based on indirect evidence from a single RCT on postmenopausal females(64).

Table 1f. Cost Analysis of Anti-Osteoporotic Drugs for the Treatment and Prevention of Fractures

Drugs	Cost per 1 fracture reduction ($)		
vs. Placebo	**Hip**	**Vertebral**	**Nonvertebral**
Alendronate	19,488	3,097	6,912
Risedronate	170,100	118,260	82,620
Ibandronate	NA	17,464	NA
Raloxifene	NA	48,564	NA
Denosumab	569,024	46,024	165,268
Teriparatide	NA	454,685	929,376
Zoledronate, generic, 4 mg	7,995	1,495	NA
Zoledronate, brand, 5 mg	135,792	25,091	NA
vs. Alendronate	**Hip**	**Vertebral**	**Nonvertebral**
Risedronate	NA	NA	NA
Ibandronate	NA	NA	NA
Raloxifene	NA	NA	NA
Denosumab	NA	141,716	NA
Teriparatide	NA	794,304	1,555,512
Zoledronate, generic, 4 mg	NA	2,294	NA
Zoledronate, brand, 5 mg	NA	74,592	NA

Adapted from the published meta-analysis of 43 RCTs in 71,809 postmenopausal females that were similar in recruitment age (mean ± SD, 67.3 ± 8.1 years) and follow-up duration (25.5 ± 12.6 months). Cost comparisons were evaluated for a treatment strategy multiplied by NNT (number needed to treat) to prevent a fracture in 1 female(60).

Table 1g. Summary of Final ICERs and Subgroups Analyzed from Articles Assessing Cost-effectiveness of Denosumab Compared with Generic Alendronate(53).

Previous Fracture	BMD	Age	Final ICER (range in 2017 US dollar)
No previous fracture	**−2.5-4**	**70+**	**Cost saving to $139,000**
No previous fracture	<−2.5	50-55	$254,000 to $260,000
Prevalent fracture	**<-2.5-4**	**50-80**	**Cost saving to $69,734**
Previous fracture	<−2.5	50-55	$196,565 to $205,187
One CRF [a]	−2.5	72+	$91,000 to $96,000
One CRF[a]	<−2.5	50-55	$175,000 to $180,000
Two CRFs[a]	−2.5	72+	$60,000 to $63,000
Two CRFs[a]	<−2.5	50-55	$118,000 to $121,000
Three CRFs[a]	−2.5	72+	$30,000 to $33,000
Three CRFs[a]	<−2.5	50-55	$63,000 to $66,000
High risk	−2.5	72+	$10,938

BMD: bone mineral density; ICER: incremental cost-effectiveness ratio.

[a] clinical risk factors (CRFs) include prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and high alcohol consumption; Cost-saving are in bold

SUMMARY OF JUDGEMENTS – IN FEMALES

	JUDGEMENT							
	Bisphosphonates	**PTHrP (abaloparatide)**	**Recombinant PTH (teriparatide)**	**RANK ligand inhibitor (Denosumab)**	**Sclerostin inhibitor (romosozumab)**	**Sclerostin inhibitor (romosozumab) to bisphosphonate (alendronate)**	**SERM (bazedoxifene)**	**SERM (raloxifene)**
DESIRABLE EFFECTS	Medium	Trivial	Small	Medium	Trivial	Small	Trivial	Small
UNDESIRABLE EFFECTS	Trivial	Trivial	Small	Trivial	Trivial	Trivial	Trivial	Trivial
CERTAINTY OF EVIDENCE	High	Moderate	Low	Moderate	Moderate	Moderate	Low	Low
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Favors the intervention	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Does not favor either the intervention or the comparison	Probably favors the intervention	Does not favor either the intervention or the comparison	Probably favors the intervention
RESOURCES REQUIRED	Negligible costs and savings	Modest costs	Large costs	Large costs	Modest costs	Modest costs	Varies	Modest costs
COST EFFECTIVENESS	Probably favors the intervention	Varies	Varies	Varies	Varies	Varies	Varies	Varies

SUMMARY OF JUDGEMENTS – IN MALES

	JUDGEMENT
	Bisphosphonates
DESIRABLE EFFECTS	Small
UNDESIRABLE EFFECTS	Trivial
CERTAINTY OF EVIDENCE	Low
VALUES	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Probably favors the intervention
RESOURCES REQUIRED	Don’t know
COST EFFECTIVENESS	Don’t know

CONCLUSIONS

Recommendation(s)

Recommendation 1a: ACP recommends that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis (strong recommendation; high-certainty evidence).

Recommendation 1b: ACP suggests that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in males diagnosed with primary osteoporosis (conditional recommendation; low-certainty evidence).

Recommendation 2a: ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; moderate-certainty evidence).

Recommendation 2b: ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in males diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; low-certainty evidence).

Recommendation 3: ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate- certainty evidence) or recombinant PTH (teriparatide, low- certainty evidence), followed by a bisphosphonate, to reduce the risk of fractures only in females with primary osteoporosis with very high risk of fracture (conditional recommendation).

Justification

Bisphosphonates should be used as first line treatment in both females and males with primary osteoporosis. In postmenopausal females and males with osteoporosis, bisphosphonates had the most favorable balance between benefits, harms, patient values and preferences, and cost among the drug classes we evaluated (Appendix 1 Tables 1a-1c) (51). However, bisphosphonates were associated with a higher risk of osteonecrosis of the jaw and atypical femoral or subtrochanteric fractures in observational studies when compared with people with osteoporosis who were not treated with bisphosphonates (low-certainty of evidence) (Appendix 1 Tables 1bi-iii) (51). In addition to net clinical benefits, bisphosphonates are much cheaper (Table) than other pharmacologic treatments and are available in generic formulations.

These recommendations are applicable to bisphosphonates studied in the eligible primary RCTs (alendronate, risedronate, or zoledronate), which were evaluated in the accompanying evidence review (51). There is no evidence that ibandronatfe reduces hip fractures (51). (65)The RANK ligand inhibitor (denosumab) can be used as a second-line treatment in both females and males at high-risk of fracture. Evidence from RCTs showed that denosumab had a favorable long-term net-benefit in postmenopausal females with primary osteoporosis, a history of osteoporotic fractures, and a history of prior treatments with bisphosphonates (Appendix 4 Table 4a) (51). Use of denosumab was not associated with a higher risk of ONJ (51); however, events were detected in the extension trials and more data are needed to clarify the risk. (51)

Benefits and Harms of Bisphosphonates

Evidence from the network meta-analysis suggested no greater benefits from other drug classes when compared with bisphosphonates (Appendix 2 Table 2a) (51). High-certainty evidence showed that bisphosphonates reduced the risk of hip fractures (absolute risk difference [ARD], 6 fewer events per 1000 patients), clinical vertebral fractures (ARD, 18 fewer events per 1000 patients), any clinical fracture (ARD, 24 fewer events per 1000 patients), and radiographic vertebral fractures

(ARD, 56 fewer events per 1000 patients) compared to placebo in RCTs assessing outcomes at least 36 months after initiation of treatment (Appendix 1 Table 1a). High-certainty evidence showed no differences between bisphosphonates and placebo in serious adverse events and withdrawals due to adverse events at least 3 years after initiation of treatment in included RCTs (Appendix 1 Table 1a) (51). However, evidence from observational studies showed that bisphosphonates were associated with a higher risk of atypical femoral fractures and osteonecrosis of the jaw (pooled from 5 observational studies adjusted RR, 3.4; 95% CI, 1.9, 5.2; low-certainty) at least 2 to 3 years after treatment initiation when compared with people with osteoporosis who were not treated with bisphosphonates (Appendix 1 Table 1b.i-iii), although observed events were not common (unadjusted incidence for osteonecrosis of the jaw: 0.01% to 0.3% of bisphosphonate users) (51). Longer treatment duration with bisphosphonates may have been associated with the higher risk of osteonecrosis of the jaw (51) and atypical femoral fractures (51). The higher risk of atypical femoral fractures was observed in Asian females when compared to non-Hispanic white females (595 vs. 109 per 100,000 person-years) (51).

When compared with other medications, evidence from RCTs suggested that there may be no differences in fracture risk reduction at ≥36 months between bisphosphonates and denosumab (low- certainty; Appendix 2 Table 2a). Raloxifene probably reduced radiographic fractures when compared with placebo but increased the risk of withdrawal due to adverse events in RCTs and was associated with the higher risk of venous thromboembolism (51). Evidence from studies with shorter follow up (12 to 36 months) showed no greater net benefit from other drug classes when compared with bisphosphonates (Appendix 2 Tables 2a-b) (51).

Benefits and Harms of the RANK Ligand Inhibitor (Denosumab)
Currently, denosumab is the only available RANK ligand inhibitor. Evidence showed that denosumab reduced clinical vertebral fractures (ARD, 16 fewer events per 1000 patients; high- certainty), probably reduced the risk of hip fractures (ARD, 4 fewer events per 1000 patients; moderate- certainty), any clinical fracture (ARD, 14 fewer events per 1000 patients; moderate- certainty) and radiographic vertebral fractures (ARD, 48 fewer events per 1000 patients; moderate- certainty) in RCTs assessing outcomes at least 3 years after initiation of treatment (Appendix 1 Table 1a). Denosumab probably reduced the risk of radiographic vertebral fractures at shorter follow-up (12 to 36 months) (ARD, 64 fewer events per 1000 patients; moderate -certainty) (Appendix 1 Table 1a).

Evidence showed there are probably no differences in serious adverse effects and withdrawal due to adverse effects at 36 months between denosumab and placebo (moderate- certainty; Appendix 1 Table 1a) or bisphosphonates in RCTs (moderate- certainty; Appendix 2 Table 2a).

Evidence showed that the benefits after 24-months of treatment with recombinant PTH (teriparatide) or the sclerostin inhibitor (romosozumab) may have outweighed harms only in a select population of postmenopausal females (mean age >74) with osteoporosis and very high-risk of fracture (Appendix 1 Table 1a and Appendix 2 Table 2a) (35, 36, 51, 66-69). We developed our recommendations based on the assessment of very high- risk of fracture in primary RCTs (36, 69). Very high-risk of fracture was based on older age and either a recent fracture (e.g., within the past 12 months), or history of multiple clinical osteoporotic fractures, or multiple risk factors for fracture (see Table 3), or failure of other available osteoporosis therapy (70-73) (Appendix 4 Table 4a).

Currently, romosozumab is the only available sclerostin inhibitor and teriparatide is the only available recombinant PTH. Discontinuation of romosozumab or teriparatide treatment may result in rapid bone loss and higher fracture risk and should be followed by administration of an antiresorptive agent (74, 75).

Since this is a conditional recommendation for females, we did not make a recommendation for males because any further downgrading due to indirectness was not sufficient to support a clinical recommendation.

Benefits and Harms of Recombinant PTH (Teriparatide)
None of the included studies evaluated the long-term benefits of teriparatide (Appendix 1 Table 1a). Evidence showed that teriparatide reduced the risk of any clinical fractures and radiographic vertebral fractures (ARD, 27 and 69 fewer, respectively, per 1000 patients; high- certainty) and may have reduced clinical vertebral fractures (ARD, 45 fewer per 1000 patients; low- certainty)when compared with placebo at 24 months of outcome assessment (51), but may have resulted in no difference in risk of hip fractures (low- certainty). Evidence from RCTs showed that teriparatide may have resulted in no difference in the risk of serious adverse effects (low- certainty) but probably increased the risk of withdrawal due to adverse effects at 36 or 24 months of follow-up (ARD, 127 or 17 more, respectively, per 1000 patients; moderate- certainty); most commonly due to nausea, dizziness, vomiting, headache, palpitations, and leg cramps (51, 76).

When compared with bisphosphonates at 24 months of outcome assessment, evidence showed that teriparatide probably reduced the risk of radiographic vertebral fractures (moderate -certainty; ARD, 66 fewer per 1000 patients), may have reduced the risk of any clinical fracture (low- certainty; ARD, 46 fewer per 1000 patients), and may have resulted in no differences in serious adverse events (low- certainty) or withdrawal due to adverse events (moderate -certainty). However, teriparatide increased the risk of withdrawal due to adverse events at longer term (36 months) (RR 3.1, low- certainty) (Appendix 2 Table 2a)(51). There is not yet sufficient evidence on the benefits and harms from sequential therapy with bisphosphonate after 72 weeks of teriparatide (51, 77)(51).

Benefits and Harms of the Sclerostin Inhibitor (Romosozumab)
None of the included studies evaluated the long-term benefits and harms of romosozumab nor did any report the impact on the risk of hip fractures (51). Moderate-certainty evidence from RCTs assessing outcomes at 12-36 months after treatment initiation showed that romosozumab probably reduced clinical vertebral (ARD, 4 fewer per 1000 patients), radiographic vertebral (ARD, 13 fewer per 1000 patients), and any clinical fracture (ARD, 9 fewer per 1000 patients) compared to placebo, but the prevention of hip fractures was not reported (Appendix 1 Table 1a) (51). At 12 months, romosozumab compared to bisphosphonates may have resulted in no differences in clinical or radiographic vertebral fractures (low certainty) with no evidence about its effect in hip fractures (51). Evidence from RCTs showed that romosozumab may have resulted in no differences in serious adverse events (moderate certainty) or withdrawals due to adverse events (low certainty) when compared to placebo (51). Romosozumab increased the risk of cardiovascular events compared to alendronate (hazard ratio, 1.9; 95% CI, 1.1,3.1) (36, 51, 78).

Benefits and Harms of the Sequential Therapy
Evidence from RCTs that looked explicitly at sequential therapy with bisphosphonates after initial treatment with denosumab, romosozumab, or teriparatide was limited (51, 78, 79). Moderate-certainty evidence from a single large RCT (36) showed that romosozumab followed by alendronate probably reduced all clinical bone fractures compared to placebo and probably reduced hip (ARD, 12 fewer per 1000 patients), clinical vertebral (ARD, 13 fewer per 1000 patients), any clinical (ARD, 33 fewer per 1000 patients), and radiographic vertebral fractures (ARD, 40 fewer per 1000 patients) compared to a bisphosphonate alone at 12-36 months of outcome assessment, without higher risk of serious harms or withdrawal due to adverse effects (Appendix 1 Table 1a and Appendix 2 Table 2a)(51).

Clinical Considerations

- Clinicians should prescribe generic medications if possible rather than more expensive brand-name medications.
- Clinicians treating adults with osteoporosis should encourage adherence to recommended treatments and healthy lifestyle modifications, including exercise, and counseling for evaluation and prevention of falls.

- Adequate calcium and vitamin D intake should be part of fracture prevention in all adults with low bone mass or osteoporosis.
- Clinicians should assess baseline risk for fracture based on individualized assessment of bone density, history of fractures, response to prior treatments for osteoporosis, and multiple risk factors for fractures (Appendix Table 3). There are many available risk assessment tools with varying predictive value which were not evaluated in the systematic review (51) or in this guideline.
- Current evidence suggests that increasing the duration of bisphosphonate therapy to longer than 3 to 5 years reduces risk for new vertebral fractures but not risk for other fractures (51, 80-82). However, there is increased risk for long-term harms (51). Therefore, clinicians should consider stopping bisphosphonates after 5 years unless the patient has a strong indication for treatment continuation
- The decision for a temporary bisphosphonate treatment discontinuation (holiday) and its duration should be individualized and should be based on baseline risk for fractures, type of medication and its half-life in bone, benefits, and harms (higher risk for fracture due to drug discontinuation).
- Females initially treated with an anabolic agent should be offered an antiresorptive agent after discontinuation to preserve gains and because of serious risk for rebound and multiple vertebral fractures.
- Older adults (for example, those aged >65 years) with osteoporosis may be at increased risk for falls and other adverse events due to polypharmacy or drug interactions. Individualized treatment selection should address contraindications and cautions for drugs indicated to treat osteoporosis based on comorbidities and concomitant medications (Appendix 1 Tables 1j-k) as well as reassessment of other drugs associated with higher risk for falls and fractures.
- There is variable risk for low bone mass in transgender persons based on age at gonadectomy, therapy with sex hormones, distribution of comorbidities, and behavioral risk factors for osteoporosis and fractures. When considering the potential risk for fractures, history of gonadectomy (including age) and sex steroid therapy should be considered in treatment decisions for secondary osteoporosis.

Subgroup considerations

Treatment effectiveness across subgroups

- Relative treatment effects did not differ by fracture risk, though risk definitions and inclusion criteria varied by study.
- There was little indication that osteoporosis treatment was more effective in participants aged ≥ 75 years.
- Most trials excluded participants with renal insufficiency or the equivalent of chronic kidney disease (CKD) stage IV or worse, but there is evidence that zoledronate, alendronate, and denosumab are effective in individuals with mild to moderate CKD. [Of note, only 1 trial distinguished patients with CKD stage IIIa (creatinine clearance 45-59 ml/min) from patients with CKD stage IIIb (creatinine clearance 30-44 ml/min), so we have very limited information about safety and efficacy in patients with moderately severe renal insufficiency].

Table 1h. Treatment effectiveness across subgroups (Treatment vs. Placebo)

Treatment	Follow-up duration	Subgroup			
		Prevalent vertebral fracture	No prevalent vertebral fracture	Prior osteoporosis treatment	Age ≥75
vs. Placebo					
Bisphosphonates	12 to < 36 months	ZOL (5, 24)[†]	Unclear	Unclear	ZOL (25), ALN (83)[§]
	≥ 36 months	ZOL (4, 84), ALN (3), RIS (85)[†]	ZOL (81, 84, 86), RIS (87)[†]	ZOL (84)* (84)	RIS (88), ZOL (84, 86)[†]
Abaloparatide	12 to < 36 months	(35, 89)[†]	(35)[†]	Unclear	(35, 90, 91)[†]

	≥ 36 months	Unclear	Unclear	Unclear	Unclear
Teriparatide	12 to < 36 months	(89)†	Unclear	Unclear	(67, 92, 93)†
		(67, 69)*			
	≥ 36 months	Unclear	Unclear	Unclear	Unclear
Denosumab	12 to < 36 months	(33)*	Unclear	Unclear	Unclear
	≥ 36 months	(64, 94)†	(34, 64, 94)†	(64)*	(64, 94)†
				(64)	
Romosozumab	12 to < 36 months	(95)*	(35, 96)†	Unclear	Unclear
	≥ 36 months	Unclear	Unclear	Unclear	Unclear
Raloxifene	12 to < 36 months	Unclear	Unclear	Unclear	Unclear
	≥ 36 months	(97)*	(97)*	Unclear	Unclear
Bazedoxifene	12 to < 36 months	Unclear	Unclear	Unclear	Unclear
	≥ 36 months	(98)*	Unclear	Unclear	Unclear

Note. In order to be listed as effective within a given subgroup, the treatment had to: be effective in improving one or more fracture outcomes in our network meta-analyses of the primary trials (i.e., a treatment that was effective in a post-hoc subgroup analysis or in a single trial, but not in the overall collection of studies analyzed, would not be listed in this table as effective) and include a population in which the majority of participants have the risk factor in question, and/or; be shown to be similarly effective in participants with and without the risk factor in question (usually through post-hoc subgroup analyses demonstrating a treatment-risk factor interaction term with P > 0.10).
Unclear indicates no studies in which the majority of participants in the parent trial had characteristic of interest, and no subgroup analyses reporting treatment effects according to characteristic of interest
Abbreviations: ALN: alendronate; RIS: risedronate; ZOL: zoledronate
**Effective, but only for radiographic vertebral fractures*
†*Effective for one or more clinical fracture outcomes*
§*Not effective for any outcome studied*

Multiple Chronic Conditions and Polypharmacy

Individualized treatment selection should address contraindications and cautions for drugs indicated to treat osteoporosis based on comorbidities and concomitant medications (Table 1j and 1k). The balance between benefits and harms would be more favorable after zoledronic acid or teriparatide in people with osteoporosis and baseline comorbid coagulation disorder (Appendix Tables 3-4).

The FDA reports drug interactions with bisphosphonates and the following: agents acting on calcium homeostasis/antacids, magnesium salts, NSAIDs, corticosteroids, diuretics, hypotensive agents, aminoglycosides, see drug labeling reports for more information.

Table 1j. Contraindications and Cautions for Bisphosphonate Based on Comorbidity and Concomitant Medications

Comorbidities, Suggested ICD codes	Alendronate	Ibandronate	Pamidronate	Risedronate	Zoledronic acid
Achalasia, K22.0	Contraindicated	Contraindicated	None reported	Contraindicated	None reported
Aspiration risk, *	Contraindicated	None reported	None reported	None reported	None reported

Renal impairment, N18	Contraindicated if CrCl <35	Contraindicated if CrCl <30	Contraindicated if CrCl <30	Contraindicated if CrCl <30	Contraindicated if CrCl <30
Esophageal stricture, K22.2	Contraindicated	Contraindicated	None reported	Contraindicated	None reported
Hypocalcemia, E83.51	Contraindicated	Contraindicated	None reported	Contraindicated	Contraindicated
Invasive dental procedure (osteonecrosis of the jaw), M87.180	None reported	Contraindicated	Contraindicated	None reported	Contraindicated
Anemia, D64.9	Caution†	Caution†	None reported	Caution†	None reported
Coagulation disorder, D68	Caution †	Caution †	None reported	Caution†	None reported
Concurrent nephrotoxic agent use, N14.1	None reported	None reported	Caution †	None reported	Caution†
Corticosteroid use	Caution †	Caution †	Caution †	Caution†	Caution†
Infection, A00- B99	Caution †	Caution†	None reported	Caution†	None reported
Malignancy, C00-D49	Caution†	Caution †	None reported	Caution†	None reported

Sources: FDA drug labels, Dynamed, IBM Micromedex, Epocrates, Reference.medscape.com/drug

*T17.21 Gastric contents in pharynx

† Caution: high risk of a discrete set of adverse reactions and other potential safety hazards that are serious or otherwise *clinically significant* because they have implications for prescribing decisions. To include an adverse event in the section, there should be reasonable causal association between the drug and the adverse event (no need for definitively established causality).

Table 1k. Contraindications and Cautions for Drugs Indicated for Fracture Prevention Based on Comorbidity and Concomitant Medications

	Monoclonal antibodies		Parathyroid hormone analogue		Selective estrogen receptor modulators
Comorbidities	**Romosozumab**	**Denosumab**	**Teriparatide**	**Abaloparatide**	**Raloxifene**
Renal impairment	CrCl <30	CrCl <30	CrCl <30	CrCl <30	CrCl <50
Calcemia	Caution: hypocalcemia	Caution: hypocalcemia	Caution: hypercalcemia	Caution: hypercalcemia	None reported
Invasive dental procedure (osteonecrosis of the jaw)	Caution	Caution	None reported	None reported	None reported
Anemia	Caution	Caution	None reported	None reported	None reported
Coagulation disorder	Caution	Caution	None reported	None reported	None reported
Corticosteroid use	Caution	Caution	None reported	None reported	None reported
Infection	None reported	Caution	None reported	None reported	None reported
Malignancy	Caution	Caution	Caution if history of skeletal malignancy	Caution if history of skeletal malignancy	None reported
Radiotherapy	Caution	None reported	Caution if history of bone radiotherapy	Caution if history of bone radiotherapy	None reported

Hereditary osteosarcoma disorders	None reported	None reported	Caution, FDA caution	Caution, FDA warning	None reported
Cardiovascular risk	Caution, FDA warning	None reported	None reported	None reported	Caution
Hepatic impairment	None reported	None reported	None reported	None reported	Caution
Stroke history or risk	Caution, FDA warning	None reported	None reported	None reported	Caution, FDA warning
Thromboembolism history or risk	None reported	None reported	None reported	None reported	Caution, FDA warning
Urolithiasis	None reported	None reported	Caution	Caution	None reported
Hypersensitivity to drug/class	Caution	Caution	Caution	Caution	Caution
Angiogenesis inhibitor use	Caution	Caution	None reported	None reported	None reported

FDA warning- Boxed warnings (formerly known as Black Box Warnings) are the highest safety-related warning that medications can have assigned by the Food and Drug Administration. These warnings are intended to bring the consumer's attention to the major risks of the drug. Medications can have a boxed warning added, taken away, or updated throughout their tenure on the market (99).

Appendix 2. EtD Framework: Treatments to Prevent Fractures in Patients with Osteoporosis, Other Treatments Compared to. Bisphosphonates

Comparative Effectiveness of Treatments to Prevent Fractures in patients with Osteoporosis vs. Bisphosphonates	
POPULATION:	Patients with Osteoporosis
INTERVENTION:	RANK ligand inhibitor (denosumab), Sclerostin inhibitor (romosozumab), Sequential Sclerostin inhibitor (romosozumab) to bisphosphonate (alendronate), PTHrP (abaloparatide), Recombinant PTH (teriparatide), SERM (bazedoxifene, raloxifene)
COMMON COMPARATOR:	Bisphosphonates
MAIN OUTCOMES:	Fractures (hip, clinical vertebral, clinical fracture, radiographic vertebral), serious adverse events, withdrawals due to adverse events, and other harms

ASSESSMENT

Desirable and undesirable effects
How substantial are the desirable and undesirable anticipated effects for each intervention?

Judgement | **Research evidence**

Desirable Effects
Large: None

Medium: None
Small:
- Romosozumab to Alendronate

Trivial:
- Abaloparatide
- Teriparatide
- Denosumab
- Romosozumab
- Bazedoxifene
- Raloxifene

Varies: None
Don't know: None
Undesirable Effects

Table 2a. Summary of Findings (SoF), Other Interventions vs. Bisphosphonates

Treatment	Relative Risk from Network Meta-analysis Certainty of Evidence Absolute Risk Difference of Events per 1,000 (provided only when direct pair-wise meta-analysis is available)					
	Fractures				Harms	
≥ 36 mo.	Hip	Clinical Vertebral	Any Clinical fracture	Radiographic Vertebral	Serious AEs*	Withdrawal due to AEs
PTHrP (abaloparatide)	---	---	---	---	---	---
Recombinant PTH (teriparatide)	---	---	---	---	0.77 (0.48,1.24) ⊕◯◯	3.11 (1.88,5.13) ⊕◯◯
RANK ligand inhibitor (denosumab)	0.94 (0.55,1.62) ⊕◯◯ --	0.82 (0.33,2.06) ⊕◯◯ --	1.03 (0.74,1.45) ⊕⊕◯ --	0.66 (0.38,1.14) ⊕◯◯ --	1.03 (0.82,1.31) ⊕⊕◯ --	1.21 (0.89,1.65) ⊕◯◯ --
Sclerostin inhibitor (romosozumab)	---	---	---	---	---	---
Sequential Sclerostin	---	---	---	---	---	---

Large: None

Medium:
- Teriparatide

Small:
- Abaloparatide
- Bazedoxifene
- Raloxifene

Trivial:
- Denosumab
- Romosozumab
- Romosozumab to Alendronate

Varies: None
Don't know: None

inhibitor (romosozumab) to bisphosphonate (alendronate)						
SERM (bazedoxifene)	1.44 (0.70,2.95) ⊕◯◯ --	1.76 (0.66,4.70) ⊕◯◯ --	1.12 (0.79,1.59) ⊕◯◯ --	1.20 (0.70,2.06) ⊕◯◯ --	1.07 (0.83,1.38) ⊕⊕◯ --	1.21 (1.04,1.41) ⊕⊕◯ --
SERM (raloxifene)	1.73 (0.95,3.18) ⊕◯◯ --	1.80 (0.83,3.89) ◯◯◯ --	1.16 (0.88,1.53) ⊕◯◯ --	1.18 (0.78,1.81) ⊕◯◯ --	1.00 (0.77,1.30) ⊕⊕◯ --	1.21 (1.05,1.39) ⊕⊕◯ --
12 to <36 mo.	**Hip**	**Clinical Vertebral**	**Any Clinical fracture**	**Radiographic Vertebral**	**Serious AEs***	**Withdrawal due to AEs**
PTHrP (abaloparatide)	---	---	0.35 (0.15,0.81) ⊕⊕◯ --	0.31 (0.11,0.88) ⊕◯◯ --	0.94 (0.65,1.37) ⊕◯◯ --	1.75 (1.17,2.61) ⊕◯◯ --
Recombinant PTH (teriparatide)	0.77 (0.18,3.25) ◯◯◯ --	0.51 (0.14,1.84) ◯◯◯ --	0.64 (0.43,0.95) ⊕◯◯ 46 fewer (72 fewer to 19 fewer)	0.43 (0.32,0.60) ⊕⊕◯ 66 fewer (100 to 32 fewer)	1.05 (0.81,1.37) ⊕◯◯ 32 more (90 fewer to 74 more)	1.31 (0.97,1.77) ⊕◯◯ 28 more (2 fewer to 57 more)
RANK ligand inhibitor (denosumab)	---	1.80 (0.17,19.02) ◯◯◯ 30 more (85 fewer to 144 more)	1.46 (0.67,3.21) ◯◯◯ 33 more (57 fewer to 123 more)	0.61 (0.31,1.21) ◯◯◯ 33 fewer (57 fewer to 123 more)	0.97 (0.63,1.50) ◯◯◯ --	2.52 (0.47,13.34) ◯◯◯ --
Sclerostin inhibitor (romosozumab)	---	0.38 (0.09,1.57) ⊕◯◯ --	0.94 (0.51,1.76) ⊕◯◯ --	0.62 (0.35,1.11) ⊕◯◯ --	1.08 (0.78,1.52) ⊕◯◯ --	0.87 (0.52,1.47) ⊕◯◯ --
Sequential Sclerostin inhibitor (romosozumab) to bisphosphonate (alendronate)	0.62 (0.42,0.91) ⊕⊕◯ 12 fewer (22 fewer to 2 fewer)	0.41 (0.22,0.75) ⊕⊕◯ 13 fewer (20 fewer to 5 fewer)	0.74 (0.63,0.89) ⊕⊕◯ 33 fewer (53 fewer to 14 fewer)	0.51 (0.39,0.66) ⊕⊕◯ 40 fewer (55 fewer to 24 fewer)	0.96 (0.74,1.24) ⊕⊕◯ 13 fewer (41 fewer to 15 more)	0.90 (0.72,1.13) ⊕⊕◯ 7 fewer (23 fewer to 8 more)
SERM (bazedoxifene)	---	---	---	---	---	---

SERM (raloxifene)	---	**0.10 (0.01,1.88)** ◯◯◯ --	**0.17 (0.03,0.81)** ⊕⊕◯ --	**0.59 (0.05,6.50)** ◯◯◯ --	**0.58 (0.21,1.63)** ◯◯◯ --	**2.58 (0.73,9.09)** ◯◯◯ --

Color key: Favors treatment; Favors comparator; No difference.
GRADE certainty of evidence: No evidence ---; Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕
*The FDA Code of Federal Regulations defines serious adverse effects as any event or reaction that results in death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect (FDA Code of Federal Regulations Title 21 (21CFR) 312.32 [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32, MedDRA (former COSTART) coding system

Additional Benefits

Quality of Life and Functional Outcomes

The 24-month VERO trial comparing teriparatide and risedronate found no significant differences in health-related quality of life.

Additional Harms

Table 2b. Additional Harms after Intervention vs. bisphosphonates

Comparison	**Atypical Femoral Fractures** **Number of Studies Sample Size** **Time of outcome assessment**	**Osteonecrosis of the Jaw** **Number of Studies Sample Size** **Time of outcome assessment**	**Atrial Fibrillation** **Number of Studies Sample Size** **Time of outcome assessment**
Head-to-Head Comparisons			
Romosozumab then alendronate vs. alendronate	1 RCT (36); N = 4,054 RCT 24 months Meta-analysis of 1 RCT; N = 4,054 RR, 0.49 (95% CI, 0.09,2.69) ◯◯◯	1 RCT (36); N = 4,054 RCT 24 months Meta-analysis of 1 RCT; N = 7,180 RR, 0.99; 95% CI, 0.06,15.77) ◯◯◯	No data
Bisphosphonates vs. raloxifene	1 observational study (38) N = 324,397 1,094,049 vs. 158,722 patient-years of continuous exposure Meta-analysis of 1 observational study; N = 324,397 aRR, 1.51; 95% CI, 1.23,1.84 ◯◯◯	3 observational studies (38-40); N = 342,842 observational 12 to 48 months (if reported) Meta-analysis of 2 observational studies; N = 332,944 aRR, 1.94; 95% CI, 0.75,12.42 ◯◯◯	2 observational studies (41, 42); N = 36,866 observational 10 to 12 months average Meta-analysis of 2 observational studies; N = 36,866 aRR, 0.83; 95% CI, 0.40,1.59 ◯◯◯
Bisphosphonates vs. raloxifene or calcitonin	1 observational study (43) N = 33,815	No data	No data

	observational mean 2.13 years (SD 2.21) Meta-analysis of 1 observational study; N = 33,815 aRR, 1.03 (95% CI, 0.70,1.52) ◯◯◯		
Bisphosphonates vs. raloxifene, calcitonin, or teriparatide	1 observational study (9) N = 5,119 observational 40 months (average) Meta-analysis of 1 observational study; N = 5,119 aRR, 0.63 (95% CI, 0.27,1.42) ◯◯◯	No data	No data
Bisphosphonate vs. denosumab	No data	No data	1 observational study (44); N = 32,470 observational NR Meta-analysis of 1 observational study; N = 32,470 aRR, 1.38; 95% CI, 1.03,1.85 ◯◯◯
Bisphosphonates vs. raloxifene or supplements (calcitonin, vitamin D, or ipriflavone)	No data	No data	1 observational study (45); N = 130,182 observational Median 4 years Meta-analysis of 1 observational study; N = 130,182 aRR, 0.52 (95% CI, 0.29, 0.91) ◯◯◯

GRADE certainty of evidence: No evidence ---; Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕
*adjusted relative risk (RR), aRR, adjusted relative risk; NR, not reported

Certainty of evidence
What is the overall certainty of the evidence of effects for each intervention?

Judgement	Research evidence	Additional considerations
High: None **Moderate:** • Romosozumab to Alendronate **Low:** • Abaloparatide • Teriparatide • Denosumab • Romosozumab • Bazedoxifene • Raloxifene **Insufficient:** None **No included studies:** None	See SoF table under "Desirable and Undesirable Effects."	N/A

Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
Judgement	**Research evidence**	**Additional considerations**
Important uncertainty or variability: None **Possibly important uncertainty or variability:** • Bisphosphonates • Abaloparatide • Teriparatide • Denosumab, • Romosozumab, • Romosozumab to Alendronate • Bazedoxifene • Raloxifene **Probably no important uncertainty or variability:** None **No important uncertainty or variability:** None	See Appendix 1 Additional public panel feedback is collected through two surveys developed ad-hoc. To date, one survey has sought the public panel's thoughts on the findings from the systematic review informing the guideline; 5 of 8 members responded. A second survey asking for the public panel's thought on the draft recommendation is planned in February 2022. • When presented with the information about medications vs. bisphosphonates, only 1 respondent indicated they would change their previous thoughts about which medications to take/recommend for treatment of *osteoporosis* identifying that some of the medications do appear to show a clear long-term advantage with little or no increased risk of SAEs or withdrawals.	

Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison for each intervention?**		
Judgement	**Research evidence**	**Additional considerations**
Favors the comparison: None **Probably favors the comparison**: • Abaloparatide • Teriparatide • Bazedoxifene • Raloxifene **Does not favor either the intervention or the comparison**: • Denosumab • Romosozumab **Probably favors the intervention**: • Romosozumab to Alendronate **Favors the intervention:** None **Varies**: None **Don't know**: None	See SoF table under "Desirable and Undesirable Effects."	N/A

Resources required How large are the resource requirements (costs) for each intervention?		
Judgement	**Research evidence**	**Additional considerations**
Large costs: • Teriparatide • Denosumab **Modest costs:** • Abaloparatide • Romosozumab • Romosozumab to Alendronate • Raloxifene **Negligible costs and savings:** None **Modest savings:** None **Large savings:** None **Varies:** None **Don't know:** Bazedoxifene	See Appendix 1.	N/A

Cost effectiveness Which intervention does the cost effectiveness favor?		
Judgement	**Research evidence**	**Additional considerations**
Favors the comparison: None **Probably favors the comparison:** None **Does not favor either the intervention or the comparison:** None **Probably favors the intervention:** None **Favors the intervention:** None **Varies:** • Abaloparatide • Teriparatide • Denosumab • Romosozumab • Romosozumab to alendronate • Bazedoxifene • Raloxifene **No included studies:** None	See Appendix 1.	N/A

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
	PTHrP (abaloparatide)	**Recombinant PTH (teriparatide)**	**RANK ligand inhibitor (Denosumab)**	**Sclerostin inhibitor (romosozumab)**	**Sclerostin inhibitor (romosozumab) to bisphosphonate (alendronate)**	**SERM (bazedoxifene)**	**SERM (raloxifene)**
DESIRABLE EFFECTS	Trivial	Trivial	Trivial	Trivial	Small	Trivial	Trivial
UNDESIRABLE EFFECTS	Small	Medium	Trivial	Trivial	Trivial	Small	Small
CERTAINTY OF EVIDENCE	Low	Low	Low	Low	Moderate	Low	Low
VALUES	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
BALANCE OF EFFECTS	Probably favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Probably favors the comparison	Probably favors the comparison
RESOURCES REQUIRED	Modest costs	Large costs	Large costs	Modest costs	Modest costs	Don’t know	Modest costs
COST EFFECTIVENESS	Varies	Varies	Varies	Varies	Varies	Varies	Varies

Subgroup considerations

Treatment effectiveness across subgroups

Teriparatide

- Direct comparative evidence that teriparatide reduces clinical fracture and vertebral fracture risk compared to bisphosphonates (VERO trial, Kendler 2018(100))
  - All participants had one or more vertebral fractures
  - 44% had one or more non-vertebral fractures
  - Most (72%) had previously been on osteoporosis medications
  - Median age 72.6
  - Baseline mean T-scores were > -2.5
- Subgroup analyses from VERO (Geusens 2018)(101) show similar effects among patients with and without prior nonvertebral fracture, with and without T-score > -2.5, and those who were and were not on bisphosphonates previously. Also, similar effects across age terciles, including those age 76.8 and greater(101).

Romosozumab to alendronate

- Direct comparative evidence that one year of romosozumab followed by one year of alendronate was more effective than two years of alendronate (36)
  - Nearly all participants had a prior osteoporotic fracture
  - Mean age 74.4
  - FRAX score 20
  - Baseline FN T-score – 2.94

Table 2c. Treatment effectiveness across subgroups (treatment vs. bisphosphonate)

		Subgroup			
Treatment	**Follow-up duration**	**Prevalent vertebral fracture**	**No prevalent vertebral fracture**	**Prior osteoporosis treatment**	**Age ≥75**
vs. Bisphosphonate					
Teriparatide vs. risedronate	12 to < 36 months	(100, 101)[†]	Unclear	(100, 101)[†]	(100, 101)[†]
Romosozumab to alendronate vs. alendronate	12 to < 36 months	(36, 100, 101)[†]	Unclear	Unclear	(36)[†]

Note. Note. In order to be listed as effective within a given subgroup, the treatment had to be effective in improving one or more fracture outcomes in our network meta-analyses of the primary trials (i.e., a treatment that was effective in a post-hoc subgroup analysis or in a single trial, but not in the overall collection of studies analyzed, would not be listed in this table as effective); and include a population in which the majority of participants have the risk factor in question; and/or be shown to be similarly effective in participants with and without the risk factor in question (usually through post-hoc subgroup analyses demonstrating a treatment-risk factor interaction term with P > 0.10).

Unclear indicates no studies in which the majority of participants in parent trial had characteristic of interest, and no subgroup analyses reporting treatment effects according to characteristic of interest

Abbreviations: ALN: alendronate; RIS: risedronate; ZOL: zoledronate
†Effective for one or more clinical fracture outcomes

Multiple Chronic Conditions and Polypharmacy

See Appendix 1.

Appendix 3. EtD Framework: Treatments to Prevent Fractures in Patients with Low Bone Mass, Treatments vs. Placebo

Should pharmacological treatment vs. no treatment (placebo) or other active treatment be used for adults with low bone mass?	
POPULATION:	Adults with low bone mass
INTERVENTION:	Pharmacological treatments
COMPARISON:	No treatment (placebo) or other active treatment
MAIN OUTCOMES:	Fractures (hip, clinical vertebral, any clinical fracture, radiographic vertebral), serious adverse events, withdrawals due to adverse events, and other harms

ASSESSMENT

Desirable and undesirable effects
How substantial are the desirable and undesirable anticipated effects?

Judgement	Research evidence
Desirable Effects ○ Trivial ● **Small** ○ Medium ○ Large ○ Varies ○ Don't know **Undesirable Effects** ○ Large ○ Medium ○ Small ● **Trivial** ○ Varies ○ Don't know	**Treatments to Prevent Fractures in patients with Low Bone Mass** Bisphosphonates are the only treatment assessed for clinical fracture risk prevention among females with low bone mass (baseline T-scores at the hip or femoral neck between -1.0 and -2.5) who are aged 65 or older included in a 6-year study with zoledronate and 18 months with alendronate (86, 102).

Table 3a. Bisphosphonates vs. placebo for low bone mass

	Benefits RR (95% CI)				Harms RR (95% CI)		
Bisphosphonates (zoledronate and alendronate)	**Hip Fracture**	**Clinical Vertebral Fracture**	**Any Clinical fractures**	**Radiographic Vertebral Fracture**	**Serious Adverse Events (SAEs)**	**Withdrawal due to Adverse Events (AEs)**	**Atrial Fibrillation**
≥ 36 mo	0.67 (0.27, 1.62) ◯◯◯	0.41 (0.22, 0.76) ⊕◯◯	0.64 (0.52, 0.79) ⊕◯◯	0.47 (0.29,0.76) ⊕◯◯	0.90 (0.81, 1.00) ⊕◯◯	0.94 (0.49, 1.82) ◯◯◯	0.98 (0.68, 1.41) ◯◯◯
12 to <36 mo.	--	--	◯◯◯	--	--	◯◯◯	--

CI: confidence interval; RR: risk ratio
Color key: Favors treatment; Favors comparator; No difference.
GRADE certainty of evidence: No evidence ---; Insufficient ◯◯◯; Low ⊕◯◯; Moderate ⊕⊕◯; High ⊕⊕⊕

The effectiveness across different individual bisphosphonates has not been directly evaluated in females with low bone mass, and evidence from subgroup analyses of studies on risedronate and denosumab reporting specific intervention effects in females with low bone mass is very uncertain (insufficient) (83, 86, 87, 103).

Certainty of evidence **What is the overall certainty of the evidence of effects?**		
Judgement	**Research evidence**	**Additional considerations**
○ Insufficient ● **Low** ○ Moderate ○ High ○ No included studies	See SoF table under "Desirable and Undesirable Effects."	N/A
Values **Is there important uncertainty about or variability in how much people value the main outcomes?**		
Judgement	**Research evidence**	**Additional considerations**
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	See Appendix 1.	

Balance of effects **Does the balance between desirable and undesirable effects favor the intervention or the comparison?**		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	See SoF table under “Desirable and Undesirable Effects.”	N/A

Resources required **How large are the resource requirements (costs)?**		
Judgement	**Research evidence**	**Additional considerations**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● **Varies** ○ Don't know	See Appendix 1.	N/A
Cost effectiveness **Does the cost-effectiveness of the intervention favor the intervention or the comparison?**		
Judgement	**Research evidence**	**Additional considerations**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No included studies.	N/A

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Medium	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Medium	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Insufficient	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

CONCLUSIONS

Recommendation

Recommendation 4: ACP suggests that clinicians take an individualized approach regarding whether to start pharmacologic treatment with a bisphosphonate in females over the age of 65 with low bone mass (osteopenia) to reduce the risk of fractures (conditional recommendation; low-certainty evidence).

Justification

Any benefits of using a bisphosphonate to reduce the risk of fractures in females with low bone mass need to be balanced with harms and costs based on an individualized assessment of the baseline risk of fractures. Diagnostic criteria in the primary studies were used to define low bone mass in females (Appendix 4 Table 4c). The effectiveness across different individual bisphosphonates has not been directly evaluated in females with low bone mass. The evidence from subgroup analyses of RCTs on risedronate and denosumab reporting specific intervention effects on bone fractures in females with low bone mass was very uncertain (insufficient evidence) (51). The systematic review did not identify any studies reporting on fracture outcomes for males with low bone mass or on differences in treatment outcomes according to sex (51). Since the certainty of evidence was low in females, further extrapolation downgraded the certainty in males to insufficient due to indirectness (51). Therefore, evidence was very uncertain to make a recommendation for or against treatment in males with low bone mass.

Benefits and Harms of Bisphosphonates (Zoledronate)

Low-certainty evidence from a long-term (6 years) single RCT of older females with a higher baseline risk of fracture (2.3%) than females with low bone mass (51, 86) showed that zoledronate may have reduced any clinical fractures and radiographic vertebral fractures, although evidence was very uncertain for the effect on hip fractures, withdrawals due to adverse events, or risk for atrial fibrillation(Appendix 3 Table 3a) (51, 86, 102). Evidence showed there may have been no differences in serious adverse events (51).

Clinical considerations

See Appendix 1.

Subgroup considerations

Males: The systematic review did not identify any studies reporting on outcomes for males with low bone mass or any evidence that would suggest outcomes associated with pharmacologic treatment would differ according to sex.

Multiple Chronic Conditions and Polypharmacy

See Appendix 1.

Appendix 4: Study population characteristics

Table 4a. Baseline characteristics in randomized trials of anti-osteoporotic drugs in adults with osteoporosis

Treatment vs. control **Author, year** **Study name** **Risk of bias**	**Study sites** **Country Enrollment years** **Trial length (*months)***	**N** **% male, if any** **Age** **Race/ethnicity*** ***(Mean (SD) or %)***	**Prior OP treatment***	**Baseline BMD T-score (*mean (SD) or %)*** **FRAX score, if reported***	**Prevalent vertebral fractures** **Other prior fractures***
12 to < 36 months					
Bisphosphonates					
Alendronate vs. placebo Orwoll, 2000 (50) N/A Low	Multicenter North America, Europe Years NR 24	241 Male: 100% Age: 63 (12) White: 99%; Other: 1%	NR	LS: -2.1 FN: -2.3 TH: -2.1	Any: 52%
Alendronate vs. placebo (alfacalcidol + calcium) Ringe, 2007 (1) AAC Trial High	Single center Germany Years NR 24	90 Male: 37% Age: 66 (9) Race/ethnicity NR	Yes % NR	LS: -3.68 (0.48) vs. -3.87 (0.41) vs. -3.65 (0.39) TH: -3.06 (0.35) vs. -3.03 (0.40) vs. -2.93 (0.37)	Mean (SD): 3.0 (1.6) Nonvertebral: 1.9 (1.3)
Alendronate vs. supplement only Zhou, 2020 (83) N/A High	Single center China 2017 18	123 Male: 75% Age: 83 (3) Asian: 100%	Yes % NR	T-scores NR BMD (g/cm2) LS: 1.13 (0.24) FN: 0.75 (0.05) TH: 0.82 (0.08)	None (excluded)
Risedronate vs. placebo Boonen, 2009 (49) N/A High	Multicenter US, Europe, AU/NZ, Lebanon Years NR 24	284 Male: 100% Age: 60 (11) White: 95%; Unknown: 4%; Asian: 1%; Hispanic: 1%; Indian: 1%	NR	LS: -3.3 (0.9)	Any: 34%
Zoledronate vs. placebo Boonen, 2012 (47) N/A Low	Multicenter Europe, S. America, Africa, AU 2006-2010 24	1199 Male: 100% Median age (range): 66 (50 to 85) < 65: 44%	Yes 2%	FN: -2.23 (0.68) TH: -1.70 (0.76)	0: 69% 1: 19% ³ 2: 12%

Treatment vs. control **Author, year** **Study name** **Risk of bias**	**Study sites** **Country Enrollment years** **Trial length (*months)***	**N** **% male, if any** **Age** **Race/ethnicity*** ***(Mean (SD) or %)***	**Prior OP treatment***	**Baseline BMD T-score (*mean (SD) or %)*** **FRAX score, if reported***	**Prevalent vertebral fractures** **Other prior fractures***
		65 to < 75: 38% ³ 75: 17% White: 94%; Black: 1%; Asian: 0.3%; Other: 4%			
Zoledronate vs. placebo Greenspan, 2015 (25) ZEST Moderate	Multicenter SNF/ALF US (PA) 2007-2012 24	197 Age: 85 (1) Race/ethnicity NR	No	LS: -0.8 (0.2) FN: -2.3 (0.1) TH: -2.1 (0.1) FRAX: TH: 9.7 (1.5) Major OP: 22.7 (1.5)	Any: 52%
Zoledronate vs. placebo Lyles, 2007 (15) HORIZON-RFT Low	Multicenter US, CA, S. America, Europe Years NR 24	2127 Male: 23% Age: 75 (10) White: 91%; Black: 1%	Yes % NR	FN ≤ -2.5: 42% -2.5 to -1.5: 33% > -1.5: 12% Missing: 12%	Any: 100%
Zoledronate vs. placebo Nakamura, 2017 (5) ZONE Moderate	Multicenter Japan Years NR 24	665 Male: 6% Age: 75 (5) Asian: 100%	Yes Previous BP use: 10%	LS: -2.87 (0.84) FN: -2.95 (0.87) TH: -2.27 (0.95)	0: 9% 1: 51% 2: 26% ≥ 3: 15%
Zoledronate vs. placebo (activated vitamin D3) Bai, 2013 (24) N/A High	Single China 2008-2010 24	483 Age: 57 (7) Race/ethnicity NR	Yes % NR (similar between groups)	FN ≤ -2.5: 43% -2.5 to -1.5: 54% ≥ -1.5: 2.5%	Previous vertebral Fx: 62%
Abaloparatide					
See Miller, 2016 under 'teriparatide'					
Denosumab					
See Anastasilakis, 2019 under 'head-to-head'					

Treatment vs. control **Author, year** **Study name** **Risk of bias**	**Study sites** **Country Enrollment years** **Trial length (*months)***	**N** **% male, if any** **Age** **Race/ethnicity*** ***(Mean (SD) or %)***	**Prior OP treatment***	**Baseline BMD T-score (*mean (SD) or %)*** **FRAX score, if reported***	**Prevalent vertebral fractures** **Other prior fractures***
Denosumab vs. placebo Nakamura, 2014 (33) DIRECT Low	Multicenter Japan Years NR 24	1011 Male: 5% Age: 70 (7) < 65: 21% 65-74: 52% ≥ 75: 27% Asian: 100%	Yes % NR	LS (L1 to L4): -2.74 FN: -2.32 TH: -1.98	0: 2% 1: 67% 2: 24% ≥ 3: 8%
Raloxifene					
Raloxifene vs. placebo Morii, 2003 (104) N/A High	Multicenter Japan Years NR 12	284 Age: 65 (6) Asian: 100%	Yes % NR	T-score NR BMD (g/cm2) LS (L2 to L4): 0.67 (0.05)	Any: 26%
See Uemura, 2020 under 'multiple drug classes'					
Romosozumab					
Romosozumab vs. placebo Cosman, 2016 (35) FRAME Low	Multicenter N. and S. America, Europe, Asia, AU Years NR 12	7180 Age: 71 (7) ≥75: 31% Hispanic: 40%	Yes % NR	LS: -2.72 (1.04) FN: -2.76 (0.28) TH: -2.48 (0.47) FRAX: 13.4 (8.8)	≥ 1: 18% Nonvertebral Fx: 22%
See Saag, 2017 under 'Multiple drug classes'					
Teriparatide					
See Hagino, 2021 under 'Head-to-head'					
Teriparatide vs. risedronate Kendler, 2018 (100) VERO Low	Multicenter N. and S. America, Europe 2012-2016 24	1366 Age: 73 (9) White: 97%; Black: 2%; Asian: 1%	Yes 72%	LS: -2.27 (1.24) FN: -2.27 (0.76) TH: -1.95 (0.87)	≥ 1: 100% 1: 34% 2: 26% 3: 15% 4: 9% ≥ 5: 16% Nonvertebral:

Treatment vs. control **Author, year** **Study name** **Risk of bias**	**Study sites** **Country Enrollment years** **Trial length (*months)***	**N** **% male, if any** **Age** **Race/ethnicity*** ***(Mean (SD) or %)***	**Prior OP treatment***	**Baseline BMD T-score (*mean (SD) or %)*** **FRAX score, if reported***	**Prevalent vertebral fractures** **Other prior fractures***
					1: 24% 2: 12% 3: 6% 4: 1% ≥ 5: 1%
Abaloparatide vs. teriparatide vs. placebo Miller, 2016 (89) ACTIVE Low	Multicenter N. and S. America, Europe, Asia 2011-2013 18	2463 Age: 69 (7) White: 81%; Black: 3%; Asian: 16%	Yes % NR	LS: -2.9 (0.9) FN: -2.2 (0.6) TH: -1.9 (0.7)	Any: 22% Nonvertebral: 30% Any Fx history: 63%
Teriparatide vs. placebo Nakamura, 2012 (67) TOWER Moderate	Multicenter Japan Years NR 17	601 Male: 5% Age: 75 (6) Asian: 100%	Yes % NR	LS: -2.7 (0.9) FN: -2.4 (0.7)	0: 10% 1: 40% 2 to 3: 35% ≥ 4: 15%
Teriparatide (20 or 40 ug) vs. placebo Neer, 2001 (69) FPT Moderate	Multicenter 99 sites in 17 countries Years NR 24	1637 Age: 70 (7) White: 98%	NR	T-score NR Adequate radiographs: LS BMD (g/cm2): 0.82 (0.17) Inadequate radiographs: LS BMD (g/cm2): 0.84 (0.16)	Mean (SD) Adequate: 2.3 (1.8) Inadequate: 2.3 (1.7)
Head-to-head: treatments vs. bisphosphonates					
Denosumab vs. zoledronate Anastasilakis, 2019 (37) AfterDmab Moderate	Multicenter Greece 2015-2016 24	60 Age: 65 (2) Race/ethnicity NR	Yes 100%	LS: -1.84 (0.15) FN: -1.68 (0.10)	Any: 26%
Romosozumab then alendronate vs. alendronate	Multicenter Europe; Middle East; Central, N. and S. America; AU/NZ; Asia-Pacific; ZA	4093 Age: 74 (8) Hispanic: 31%	Yes % NR	LS: -2.94 (1.25) FN: -2.89 (0.49) TH: -2.78 (0.68) FRAX: 20.2 (10.2)	Any: 96% Previous osteoporotic Fx ≥ age 45: 99%

Treatment vs. control **Author, year** **Study name** **Risk of bias**	**Study sites** **Country Enrollment years** **Trial length (*months)***	**N** **% male, if any** **Age** **Race/ethnicity*** ***(Mean (SD) or %)***	**Prior OP treatment***	**Baseline BMD T-score (*mean (SD) or %)*** **FRAX score, if reported***	**Prevalent vertebral fractures** **Other prior fractures***
Saag, 2017 (36) ARCH Low	Years NR 24 (12 double-blind, 12 open-label)				Previous nonvertebral Fx ≥ 45: 38% Previous hip Fx: 9%
≥ 36 months					
Bisphosphonates					
Alendronate vs. placebo Black, 1996 (3) FIT Low	Multicenter US Recruitment completed in 1993 36	2027 Age: 71 (6) 75 to 81: 26% 65 to 74: 57% < 65: 17% White: 97%; Asian: 1%; AA/Black: 1%	No	T-score NR BMD (g/cm2) FN: 0.57 (0.07) Posterior-anterior spine: 0.79 (0.14)	1: 70% 2: 17% ≥ 3: 13% History of post-menopausal Fx: 57%
Alendronate vs. placebo Cummings, 1998 (105) FIT Low	Multicenter US Years NR 48	4432 Age: 67 (6) < 65: 35% 65 to 74: 53% 75 to 80: 13% Race/ethnicity NR	No	FN > -2.5: 37% -2.0 to -2.5: 33% -1.5 to -2.0: 30%	Fx history since age 45: 36%
Alendronate vs. alfacalcidol Ringe, 2004 (46) N/A Moderate	Single site Germany Years NR 36	134 Male: 100% Age: 52.1 (10.9) Race/ethnicity NR	Yes, with washout % NR	LS: -3.42 FN: -2.53	Prevalent vertebral Fx: 79% vs. 80%
Ibandronate (0.5 or 1 mg) vs. risedronate Nakamura, 2013 (106) MOVER Moderate	Multicenter Japan Years NR 36	1265 Male: 5% Age: 73 (6) ≥75: 42% Asian: 100%	Yes % NR	LS (L2 to L4): -2.71 (1.01) FN: -2.48 (0.73) TH: -2.17 (0.87)	1: 50% 2: 26% > 2: 25%

Treatment vs. control **Author, year** **Study name** **Risk of bias**	**Study sites** **Country Enrollment years** **Trial length (*months)***	**N** **% male, if any** **Age** **Race/ethnicity*** ***(Mean (SD) or %)***	**Prior OP treatment***	**Baseline BMD T-score (*mean (SD) or %)*** **FRAX score, if reported***	**Prevalent vertebral fractures** **Other prior fractures***
Ibandronate vs. placebo Chesnut, 2004 (107) BONE Moderate	Multicenter Europe and N. America Years NR 36	2946 Age: 69 (6) Other demographics NR	No BPs, otherwise, NR	LS: -2.8 (0.9) FN: -2.0 (0.9) TH: -1.7 (0.9)	1: 94% 2: 44%
Risedronate vs. placebo Reginster, 2000 (108) VERT MN High	Multicenter (80) Europe and AU Years NR 36	1226 Age: 71 (7) Race/ethnicity NR	Yes % NR	LS: -2.84 (1.39)	Median/pt. (range): 4 (0 to 13)
Risedronate vs. placebo Harris, 1999 (85) VERT NA Low	Multicenter North America 1993-1998 36	2458 Age: 69 (8) Race/ethnicity NR	No	LS: -2.4 (1.4) FN: -2.7 (1.1)	Any: 80% Mean (SD): 2.5 (0.1)
Zoledronate vs. placebo Lu, 2021 (2) N/A High	Single site China 2013-2018 36	188 Male: 19.2% Age: 68.7 100% Asian	No	T-scores NR left FN BMD g/cm2: 0.51 (0.11)	NR
Zoledronate vs. placebo Reid, 2018 (86) N/A Low	Multicenter (community-based) NZ 2009-2011 72	2000 Age: 71 (5) European: 95%; Māori: 2%; East Asian: 2%	Yes % NR	LS: -0.91(1.12) FN: -1.64 (0.47) TH: -1.27 (0.59)	Any: 14% Nonvertebral: 24%
Zoledronate vs. placebo Black, 2007 (4) HORIZON-PFT Low	Multicenter US, CA, Europe, Asia, S. America 2002-2006 36	7765 Age: 73 (5) < 70: 30% 70 to 74: 32% ≥ 75: 39% Race/ethnicity NR	Yes 21% both groups	FN < -2.5: 73% -2.5 to -1.5: 26% > -1.5: 1% Missing: 0.6%	0: 38% 1: 28% 2+: 34% Missing: < 0.1%
Bazedoxifene					

Treatment vs. control **Author, year** **Study name** **Risk of bias**	**Study sites** **Country Enrollment years** **Trial length (*months)***	**N** **% male, if any** **Age** **Race/ethnicity*** ***(Mean (SD) or %)***	**Prior OP treatment***	**Baseline BMD T-score (*mean (SD) or %)*** **FRAX score, if reported***	**Prevalent vertebral fractures** **Other prior fractures***
Bazedoxifene (20 or 40 mg) vs. raloxifene vs. placebo Silverman, 2008 (109) N/A Low	Multicenter Asia-Pacific, CA, ZA, US, Europe, Latin America Years NR 36	7492 Age: 67 (7) White: 88%	Yes % NR	LS: -2.4 (1.2) FN: -1.7 (0.9)	Any: 56%
Denosumab					
Denosumab vs. placebo Cummings, 2009 (34) FREEDOM Moderate	Multicenter US, CA, UK, Europe, S. America, AU/NZ Years NR 36	7868 Age: 72 (5) < 70 y: 26% 70-74 y: 42% ≥ 75 y: 32% Race/ethnicity NR	Yes % NR	LS: -2.82 (0.70) FN: -2.15 (0.72) TH: -1.89 (0.81)	Any: 24% Missing: 3%
Raloxifene					
Raloxifene vs. placebo Group 1: T-score < -2.5 Group 2: low BMD + FX history Ettinger, 1999 (110) MORE Moderate	Multicenter 180 sites in 25 countries 1994-1997 36 for primary outcomes; 40 for SAEs	7705 Group 1: Age: 65 (7) Group 2: Age: 68 (7) Race/ethnicity NR	Yes Previous estrogen therapy: Group 1: 29% Group 2: 27%	T-scores NR Hologic densitometry: Group 1: FN: 0.59 (0.06) LS: 0.77 (0.11) Group 2: FN: 0.57 (0.07) LS: 0.75 (0.13)	Group 1: 0: 89% 1: 10% ≥ 2: 2% Group 2: 0: 10% 1: 40% ≥ 2: 50%
See Silverman, 2008 under 'bazedoxifene'					
Teriparatide					
Teriparatide vs. placebo Fujita, 2014 (68) N/A Moderate	Multicenter Japan 1999-2002 36	329 Male: 8% Age: 72 (7) Race/ethnicity NR	Yes % NR	LS: -2.80 (1.10)	1: 39% 2: 24% 3: 37%

*Only treatment group characteristics are reported unless significant between-group difference existed, in which case reported as treatment vs. control

Abbreviations: AU: Australia; BMD: bone mineral density; CA: Canada; FN: femoral neck; Fx: fracture; HRT: hormone replacement therapy; LS: Lumbar spine; N/A: not applicable; NR: not reported NZ: New Zealand; OP: osteoporosis; PA: Pennsylvania; RoB: Risk of Bias; SD: standard deviation; TH: total hip; UK: United Kingdom; US: United States; ZA: South Africa
1 RCT enrolled subjects in long-term care facilities (25)

Table 4b. Baseline Characteristics in Osteoporosis RCTs that Included Males

Treatment vs. Control **Author, Year** **Study Name** **Total Sample Size (N)** **Risk of Bias**	**Study sites** **Country** **Years of Enrollment** **Follow-up**	**Prior Osteoporosis Treatment Treated (%)**	**Demographics** **% Male, if applicable** **Age: Mean (SD)** **% Patients by Age Group** **Race/Ethnicity**	**Baseline mean BMD T-scores (SD)** **Lumbar Spine, Femoral Neck, Total Hip** **Treatment vs. Control**	**Prevalent vertebral fractures** **Other prior fractures, if applicable** **Treatment vs. Control**
Bisphosphonates in RCTs that enrolled all males					
Alendronate vs. placebo Orwoll, 2000(50) N/A N = 241 Low	Multicenter North America, Europe	NR	Male: 100% Age: 63 (12) vs. 63 (13) White: 99 vs. 97% Other: 1 vs. 3%	LS: -2.1 vs. -2.0 FN: -2.3 vs. -2.2 TH: -2.1 vs. -2.1	Any vertebral fx: 52% vs. 49%
Alendronate vs. alfacalcidol Ringe, 2004(46) N/A N = 134 Moderate	Single site Germany Years NR 36 months	Yes, with washout % NR	Male: 100% Age: 52.1 (10.9) vs. 53.3 (11.1) Race/ethnicity NR	LS: -3.42 vs. -3.35 FN: -2.53 vs. -2.56	Prevalent vertebral fracture: 79% vs. 80%
Risedronate vs. placebo Boonen, 2009(49) N/A N = 284 High	Multicenter US, Europe, Australia/New Zealand, Lebanon 24 months	NR	Male: 100% Age: 60 (11) vs. 62 (11); P = 0.28 White: 95% vs. 95% Unknown race: 4% vs. 2% Asian: 1% vs. 1% Hispanic: 1% vs. 1% Indian: 1% vs. 1%	LS: -3.3 (0.9) vs. -3.1 (0.9); P = .31	Any: 34% vs. 35%
Zoledronate vs. placebo Boonen, 2012(47) N/A	Multicenter Europe, South America, Africa, Australia	Yes 1.9 vs. 1.3%	Male: 100% Age: 66 vs. 66 < 65: 44.2 vs. 46.5	FN: -2.23 (0.68) vs. -2.24 (0.69) TH: -1.70 (0.76) vs. -1.72 (0.81)	0: 68.7% vs. 66.9% 1: 19.4% vs. 22.1% [3] 2: 11.7% vs. 10.8%

Treatment vs. Control **Author, Year** **Study Name** **Total Sample Size (N)** **Risk of Bias**	**Study sites** **Country** **Years of Enrollment** **Follow-up**	**Prior Osteoporosis Treatment Treated (%)**	**Demographics** **% Male, if applicable** **Age: Mean (SD)** **% Patients by Age Group** **Race/Ethnicity**	**Baseline mean BMD T-scores (SD)** **Lumbar Spine, Femoral Neck, Total Hip** **Treatment vs. Control**	**Prevalent vertebral fractures** **Other prior fractures, if applicable** **Treatment vs. Control**
N = 1199 Low	2007-2008 24 months		65 to < 75: 38.4 vs. 34.9 [3] 75: 17.3 vs. 18.7 White: 94.4 vs. 94.6% Black: 0.9 vs. 0.5% Asian: 0.3 vs. 0.0%		
Bisphosphonates in RCTs that enrolled males					
Alendronate vs. placebo (alfacalcidol + calcium) Ringe, 2007 (1) AAC Trial N = 90 High	Single Germany Years NR 24 months	Yes % NR	Male: 36.7% vs. 36.7% Age: 65.7 (9.44) vs. 65.9 (7.63) vs. 66.4 (9.51) Other NR	LS: -3.68 (0.484) vs. -3.87 (0.406) vs. -3.65 (0.390) Hip: -3.06 (0.346) vs. -3.03 (0.404) vs. -2.93 (0.374)	Mean (SD) 3.0 (1.55) vs. 3.1 (1.60) vs. 3.1 (1.57) Nonvertebral fractures: 1.9 (1.28) vs. 2.0 (1.13) vs. 1.8 (1.18)
Alendronate vs. supplement only (not blinded) Zhou, 2020(83) N/A N = 123 High	Single center China 2017 18 months	Yes % NR	Male: 74.8% Age: 83.16 (3.09) vs. 83.82 (2.85) 100% Asian	T-scores NR BMD in g/cm2 LS: 1.129±0.241 vs. 1.217 ±0.237 FN: 0.746±0.054 vs. 0.793±0.079 Hip: 0.822±0.082 vs. 0.871±0.104	None (excluded)
Ibandronate (0.5 or 1 mg) vs. Risedronate Nakamura, 2013(106) MOVER N = 1265 Moderate	Multi-site Japan 36 months	Yes % NR	Male: 5.3% vs. 7.3% vs. 8.8% Age: 72.9 (6.34) vs. 72.2 (6.38) vs. 73.0 (6.29) ≥75: 41.8% vs. 35.9% vs. 39.6% 100% Asian	LS (L2–L4): -2.71 (1.01) vs. -2.68 (1.01) vs. -2.59 (1.06) FN: -2.48 (0.73) vs. -2.41 (0.80) vs. -2.53 (0.79) Hip: -2.17 (0.87) vs. -2.09 (0.86) vs. -2.18 (0.86)	1: 49.5% vs. 48.2% vs. 48.7% 2: 25.8% vs. 27.7% vs. 25.3% >2: 24.7% vs. 24.1% vs. 26.1%
Zoledronate vs. placebo Lu, 2021 (2) N/A N = 188	Single site China 2013-2018 36 months	No	Male: 19.2 vs. 19.7%; P = 0.94 Age: 68.7 (9.3) vs. 70.8 (9.1); P =0 .30	T-scores NR left FN BMD g/cm2: 0.51 (0.11) vs. 0.51 (0.11); P = 0.91	NR

Treatment vs. Control **Author, Year** **Study Name** **Total Sample Size (N)** **Risk of Bias**	**Study sites** **Country** **Years of Enrollment** **Follow-up**	**Prior Osteoporosis Treatment Treated (%)**	**Demographics** **% Male, if applicable** **Age: Mean (SD)** **% Patients by Age Group** **Race/Ethnicity**	**Baseline mean BMD T-scores (SD)** **Lumbar Spine, Femoral Neck, Total Hip** **Treatment vs. Control**	**Prevalent vertebral fractures** **Other prior fractures, if applicable** **Treatment vs. Control**
High			100% Asian		
Zoledronate vs. placebo Lyles, 2007(15) HORIZON-RFT N = 2127 Low	Multicenter US, Canada, South America, Europe 24 months	Yes % NR	Male: 23.3% vs. 24.5% Age: 74.4 (9.48) v 74.6 (9.86) White: 91.4 vs. 90.9% Black: 0.6 vs. 1.0%	FN ≤ -2.5: 42.3 vs. 41.1% -2.5 to -1.5: 33.8 vs. 35.3% > -1.5: 11.5 vs. 11.4% missing: 12.3 vs. 12.1%	Any: 100%
Zoledronate vs. placebo Nakamura, 2017 (5) ZONE N = 665 Moderate	Multicenter Japan enrollment period not specified 24 months	Yes Previous bisphosphonate use: 9.7% vs. 8.5%	Male: 6.4% vs. 5.7% Age: 74.9 (5.4) vs. 74.3 (5.4) 100% Asian	LS: -2.87 (0.84) vs. -2.97 (0.83) FN: -2.95 (0.87) vs. -2.94 (0.85) Hip: -2.27 (0.95) vs. -2.20 (0.89)	0: 8.8% vs. 10.6% 1: 50.6% vs. 48.6% 2: 26.1% vs.25.4% 3+: 14.5% vs. 15.4%
PTH analogue					
Teriparatide vs. placebo Fujita, 2014 (68) N/A N = 329 Moderate	Multicenter Japan 1999-2002 36 months	Yes % NR	Male: 7.7% vs. 6.3%; P = 0.53 Age: 71.6 (6.7) vs. 71.3 (6.9); P = 0.91 Race NR	LS: -2.80 (1.10) vs. -3.02 (0.88); P = 0.18	1: 39.3% vs. 38.5% 2: 24.0% vs. 34.3% 3: 36.7% vs. 27.3% P = 0.53
Teriparatide vs. placebo Nakamura, 2012 (67) TOWER N = 601 Moderate	Multi-site Japan Years NR 72 weeks	Yes % NR	Male: 4.5% vs. 3.4% Age: 75.1 (5.8) vs. 75.5 (5.8) 100% Asian	LS: -2.7 (0.9) vs. -2.6 (0.9) FN: -2.4 (0.7) vs. -2.4 (0.8)	0: 10.1% vs. 12.2% 1: 40.2% vs. 41.6% 2-3: 35.0% vs. 35.0% ≥4: 14.7% vs. 11.2%
RANK ligand inhibitor					
Denosumab vs. placebo Nakamura, 2014 (33) DIRECT N = 500 vs. 511 Low	Multicenter Japan Years NR 24 months	Yes % NR	Male: 4.9% vs. 5.0% Age: 69.9 (7.36) vs. 69.0 (7.67) <65: 21.0% vs. 26.3% 65-74: 52.1% vs. 48.1% 75+: 26.9% vs. 25.6% 100% Japanese	LS (L1-L4): -2.78 (0.89) vs. -2.73 (0.88) Femoral neck: -2.38 (0.70) vs. -2.29 (0.71) Hip: -2.01 (0.79) vs. -1.95 (0.73)	0: 1.3% vs. 1.9% 1: 66.7% vs. 66.5% 2: 23.9% vs. 21.9% 3+: 8.1% vs. 9.8%

Abbreviations: BMD: bone mineral density; NR: not reported; SD: standard deviation

Table 4c. Baseline characteristics in randomized trials of bisphosphonates in adults with low bone mass compared with placebo

Drug RCTs Total sample	Demographics (ranges) % males Age: Mean Race/ethnicity: % Residence	Baseline BMD T-score Concomitant osteoporosis treatment	Prior fractures Prior osteoporosis treatment	Baseline risk of fracture Inclusion Criteria Exclusion Criteria
Zoledronate vs. placebo				
Zoledronate (86) 1 RCT of 2000 subjects	95% European Residing in long-term care facilities 0%	Baseline BMD T-score L-Spine: -0.91 (1.12) Advice for dietary intake of calcium 1 gram/day and vitamin D (2.5 mg to 1.25mg cholecalciferol)	Nonvertebral fractures in 24% Vertebral fractures in 14% No bone active drugs in past year	Low baseline risk of fracture Eligible: postmenopausal females 65 years or older, with osteopenia Excluded: comorbidities resulting in secondary osteoporosis, prior anti-osteoporotic medications

Appendix 5: Detailed Methods of the Systematic Review and Guideline

Details of the ACP guideline development process can be found in ACP's methods articles (111, 112).

Panel Composition and Stakeholder Involvement

The CGC is a multidisciplinary group of 14 members. Twelve of these members are internal medicine physicians representing various clinical areas of expertise across hospital and ambulatory medicine, including internal medicine subspecialties (for example, geriatrics, nephrology, rheumatology, pulmonology, and hospital medicine). The development of this guideline also included perspectives, values, and preferences of 2 nonphysician CGC members who represent the public and a 7-member CGC Public Panel. The CGC convened a technical expert panel made up of clinical topic experts, clinicians, and epidemiologists to inform the systematic review and assist in refining the scope and key questions.

Disclosures of Interests and Management of Conflicts of Interest

All financial and intellectual disclosures of interest were declared, and potential conflicts were discussed and managed in accordance with CGC policy (112). Disclosure of interests and management of any conflicts can be found on ACP's website (https://www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm).

Key Questions and Clinical Outcomes of Interest

The CGC identified the key questions (Table 5a). Members of the CGC (clinicians and non clinician public members) and the CGC Public Panel members were asked a priori to independently rate the importance of evaluated outcomes (Table 5b). All critical and important outcomes were considered in developing recommendations.

Table 5a. List of Key Questions

Key Questions
KQ 1. What are the effects of pharmacologic interventions on fracture-related outcomes in females with low bone mass?
KQ 2. What are the effects of pharmacologic interventions on fracture-related outcomes in males with low bone mass?
KQ 3. What are the comparative effects of pharmacologic treatments on fracture related outcomes in females with osteoporosis?
KQ 4. What are the comparative effects of pharmacologic treatments on fracture related outcomes in males with osteoporosis?
KQ 5. What are the harms of pharmacologic therapy used to treat low bone mass or osteoporosis?
KQ 6. What are the effects of pharmacologic therapy compared to non-pharmacologic therapy (such as exercise) on fracture related outcomes in patients with low bone mass or osteoporosis?
KQ 7. What are patients' values and preferences on osteoporosis prevention and treatment? How do patients with low bone mass or osteoporosis weigh the benefits and harms of pharmacologic and non-pharmacological interventions for fracture prevention? How do patients use this valuation in their decision-making regarding treatment?
KQ 8. What are the costs and cost-effectiveness of pharmacologic interventions used to reduce fracture-related outcomes in males and females with low bone mass or osteoporosis?

Systematic Review

This guideline is based on an accompanying systematic review and network meta-analysis done by the ACP Center for Evidence Review at the Portland Veteran Affairs Research Foundation and funded by ACP (51).

Values & Preferences
The accompanying systematic reviewer included systematic reviews on patient values and preferences In addition, ACP staff surveyed the CGC Public Panel to assess their preferences regarding the intervention options, through two surveys developed ad-hoc to collect public panel's thoughts on the findings from the systematic review informing the guideline; and to ask for their thought on the draft recommendations.

Costs
The CER included systematic reviews on costs or cost-effectiveness. The ACP staff also searched several commercial and government databases to find drug cost from patient and societal perspectives.

Clinical Considerations
Clinical considerations summarize information that is pertinent to implementation of the recommendations, but they do not inform the development of the recommendations. Since clinical considerations may go beyond the scope of the key questions, additional references outside the scope of the systematic review may be incorporated. This evidence may be identified in other existing systematic reviews, reference lists of included primary studies, or reference works shared by the Technical Expert Panel.

Peer Review
The supporting systematic review and guideline each underwent a peer review process through the journal. The guideline was posted online for comments from ACP Regents and ACP Governors, who represent internal medicine and its subspecialty physician members at the national and international level. The CGC considered any comments before finalizing the guideline.

Guideline Expiration or Living Guideline Process
The CGC intends to maintain this topic as living. Quarterly literature surveillance is planned to identify and evaluate new evidence from published randomized controlled trials, and both the guideline and systematic review will be periodically updated.

Table 5b. Outcome Ratings

Outcomes Rated as Critical	Outcomes Rated as Important
• **Reduction in fractures (prioritized hip, followed by clinical vertebral, then any clinical, then radiographic vertebral)** • **Functional status** • **Quality of life** • **Serious adverse events**	• **Withdrawals due to adverse events**
Outcome prioritization	
When evaluating the net benefits of the various treatments, we looked at rates of bone fractures at longer (≥36 months) and shorter time of outcome assessment (12 to < 36 months) (54). The CGC prioritized benefits and harms that lasted ≥36 months, and cost-effectiveness from all oral and injectable medications regardless of treatment duration (51). Each study contributed to outcomes at one time point of fracture assessment (at 12 to < 36 months or ≥36 months). In addition, we prioritized the prevention of hip fractures and clinical vertebral fractures followed by the prevention of any clinical or radiographic vertebral fractures based on the high risk of disability, institutionalization, morbidity, and mortality in people with clinical fractures (55, 56) and the high risk of future fractures in people with radiographic fractures (57). Appendix Table 2 presents definitions of each fracture category.	

We also prioritized serious adverse events reported in randomized controlled trials (RCTs) and observational studies as more clinically important than withdrawals due to adverse events usually available from RCTs only. Overall, we contextualized the balance between benefits and harms based on the direction and the magnitude of treatment effects across all outcomes and considering the certainty of evidence.

Table 5c. Ongoing Studies

The CER searched ClinicalTrials.gov for potentially eligible studies in November 2021. The CER has highlighted those ongoing studies that have recently completed or are due to complete soon and could be published for inclusion in an updated evidence review, depending on the date of that review.

The CER identified 14 ongoing studies that would potentially be eligible for inclusion in an updated review: 9 RCTs and 5 NRSs

Of these 14 ongoing studies, 1 published a journal article in 2021(113)

Table 5c Potentially Eligible Ongoing Studies

NCT Identifier Study Name	Enrollment Population	Treatment Groups	Follow-up	Eligible Outcomes	Primary Completion Date	Status
RCTs						
NCT02589600**(114)** ZEST II	N = 310 (actual) Females aged 65 and older living in long-term care facilities and who have osteoporosis	• Zoledronic acid, in combination with vitamin D and calcium supplements • Vitamin D and calcium supplements	Up to 3 years	• Non-traumatic incident fractures (vertebral and nonvertebral)	September 2022 (estimated)	Ongoing
NCT03293108**(115)** Not reported	N = 190 (estimated) Females post menopause with osteoporosis	• Denosumab biosimilar (Arylia), in combination with vitamin D and calcium supplements • Denosumab (Amgen), in combination with vitamin D and calcium supplements	Up to 18 months	• Vertebral fractures • AEs	September 2020 (estimated)	Ongoing Primary completion date passed No results posted No publication identified

NCT Identifier Study Name	Enrollment Population	Treatment Groups	Follow-up	Eligible Outcomes	Primary Completion Date	Status
NCT03868033**(116)** DST	N = 100 (estimated) Females post menopause and males aged over 50 on denosumab for at least 2 years for osteoporosis	• Denosumab for 2 years • Zoledronic acid for 1 year followed by denosumab for 1 year • Zoledronic acid for 2 years • Zoledronic acid for 1 year with additional treatment if bone turnover is increased	Up to 2 years	• Clinical osteoporotic fracture	December 2022 (estimated)	Ongoing
NCT04591275**(117)** Not reported	N = 278 (estimated) Females post menopause with osteoporosis and at high risk of fracture	• Biosimilar denosumab (CMAB807), in combination with vitamin D and calcium supplements • Denosumab (Prolia), in combination with vitamin D and calcium supplements	Up to 12 months	• New osteoporotic fractures • AEs • SAEs	January 2023 (estimated)	Ongoing

NCT Identifier Study Name	Enrollment Population	Treatment Groups	Follow-up	Eligible Outcomes	Primary Completion Date	Status
NCT04719572**(118)** Not reported	N = 180 (estimated) Females post menopause and males aged 50 and older with osteoporosis or osteopenia	• Alendronate, zoledronate, tripopeptide, denosumab, activated vitamin D, menatetrenone soft capsules, according to the patient's condition, in combination with vitamin D and calcium supplements • Lifestyle changes (diet, exercise) and rehabilitation, in combination with vitamin D and calcium supplements • Vitamin D and calcium supplements	Up to 12 months	• Fracture rate • AEs	September 2022 (estimated)	Ongoing
NCT04729621**(119)** Not reported	N =326 (estimated) Females post menopause with osteoporosis	• Biosimilar denosumab (TVB-009) • Denosumab (Prolia), followed by biosimilar denosumab (TVB-009) • Denosumab (Prolia)	Up to 78 weeks	• Fractures • AEs • Withdrawals due to AEs	June 2023 (estimated)	Ongoing

NCT Identifier Study Name	Enrollment Population	Treatment Groups	Follow-up	Eligible Outcomes	Primary Completion Date	Status
NCT05058443**(120)** Not reported	N = 120 (estimated) Adults who had vertebral kyphoplasty for osteoporotic vertebral compression fractures	• Denosumab • Placebo	Up to 12 months	• Disability • Health-related quality of life	March 2022 (estimated)	Ongoing
NCT05065164**(121)** Not reported	N = 125 (estimated) Adults who had screw internal fixation of osteoporotic vertebral compression fracture	• Denosumab • Placebo	Up to 12 months	• Disability • Health-related quality of life	March 2022 (estimated)	Ongoing
NCT05087030**(122)** Not reported	N = 434 (estimated) Females post menopause with osteoporosis	• Biosimilar denosumab (RGB-14-P) • Denosumab (Prolia)	Up to 78 weeks	• Vertebral fragility fracture • Nonvertebral fragility fracture • AEs	June 2023 (estimated)	Ongoing
Nonrandomized Studies						
NCT01416194**(123)** Not reported	N = 10,497 (actual) Females aged 45 and over with osteoporosis who have records of receiving bazedoxifene, bisphosphonates or raloxifene	• Bazedoxifene • Bisphosphonates • Raloxifene	Up to a maximum of 92.1 months	• VTE • Ischemic stroke • Cardiac disorders • AF • Biliary events • Hypertriglyceridemia • Renal failure • Malignancies • Depression • Ocular events • Thyroid disorders-goiter	April 2019 (actual)	Ongoing Primary completion date passed Results posted on CT.gov in May 2020 No publication identified

NCT Identifier Study Name	Enrollment Population	Treatment Groups	Follow-up	Eligible Outcomes	Primary Completion Date	Status
NCT01967160**(124)** Not reported	N = 2,560 (actual) People with cancer treated with antiresorptive therapies for skeletal-related event prevention	• Denosumab • Zoledronic acid	Up to 5 years	• Osteonecrosis of the jaw • Infection leading to hospitalization	August 2019 (actual)	Published in 2021 by Ehrenstein et al.**(113)**
NCT02304887**(125)** Not reported	N = 1,000 (estimated) Adults aged 45 and over with osteoporosis	• Bisphosphonates • Teriparatide • Denosumab	Up to 10 years	• Renal function	December 2018 (estimated)	Ongoing Primary completion date passed No results posted No publication identified
NCT02520362**(126)** Not reported	N = 508,215 (estimated) Females post menopause Females post menopause with osteoporosis Males with osteoporosis Patients who receive denosumab for unapproved indications	• Bisphosphonates • Denosumab	Up to 10 years	• Osteonecrosis of the jaw • Atypical femoral fracture • Fracture healing complications • Hypocalcemia • Infection • Dermatologic AEs • Acute pancreatitis • Hypersensitivity • New primary malignancy	March 2024 (estimated)	Ongoing

NCT Identifier Study Name	Enrollment Population	Treatment Groups	Follow-up	Eligible Outcomes	Primary Completion Date	Status
NCT04974723**(127)** Not reported	N = 16,000 Females post menopause new to anabolic therapies	• Abaloparatide • Teriparatide	Up to 18 months	• Time to a composite of nonfatal MI, nonfatal stroke, or in-hospital cardiovascular death • Time to a composite of nonfatal MI, nonfatal stroke, heart failure, or in-hospital cardiovascular death	August 2021 (estimated)	Ongoing Primary completion date passed No results posted No publication identified

RCT Duplication Using Real World Data

The CER also identified 2 studies designed to duplicate 2 pivotal RCTs in osteoporosis (HORIZON and VERO) using health care claims data. The CER has not highlighted these as being eligible studies, as they are not RCTs of effectiveness, and as such, do not meet the inclusion criteria. However, they are nonrandomized duplicates of pivotal osteoporosis RCTs, so the CER has included them for information.

NCT Identifier Study Name	Enrollment Population	Treatment Groups	Follow-up	Eligible Outcomes	Primary Completion Date	Status
NCT04736693**(128)** Not reported	N = 18,028 (actual) Females post menopause with osteoporosis	• Raloxifene • Zoledronic acid	Up to 540 days	• Hip fracture • Nonvertebral fracture	February 2021 (actual)	Ongoing Primary completion date passed No results posted No publication identified
NCT04879420**(129)** Not reported	N = 12,757 (actual) Females post menopause with osteoporosis	• Teriparatide • Risedronate	Up to 730 days	• New vertebral fractures • Nonvertebral fractures	June 2021 (estimated)	Ongoing Primary completion date passed No results posted

NCT Identifier Study Name	Enrollment Population	Treatment Groups	Follow-up	Eligible Outcomes	Primary Completion Date	Status
						No publication identified

Abbreviations. AE: adverse event; AF: atrial fibrillation; NCT: US National Clinical Trial; RCT: randomized controlled trial; SAE: serious adverse event; VTE: venous thromboembolism.

Notes

- Excluded people with anorexia nervosa (assumed to be secondary osteoporosis)
- Excluded people post renal transplant (assumed to be secondary osteoporosis)
- Excluded people with breast cancer (assumed to be secondary osteoporosis)
- Excluded studies that completed over 3 years ago, without any identified publications
- Excluded studies measuring bone mass density alone
- Excluded RCTs with only outcomes of interest being safety
- Excluded comparisons of generic vs. brand formulations
- Excluded comparisons of branded formulations

References

1. Ringe JD, Farahmand P, Schacht E, Rozehnal A**.** Superiority of a combined treatment of Alendronate and Alfacalcidol compared to the combination of Alendronate and plain vitamin D or Alfacalcidol alone in established postmenopausal or male osteoporosis (AAC-Trial). Rheumatol Int. 2007;27(5):425-34. [PMID: 17216477] doi: 10.1007/s00296-006-0288-z
2. Lu K, Yin Y, Li C, Jin Y, Shan HQ**.** Efficacy of annual zoledronic acid in initial percutaneous kyphoplasty patients with osteoporotic vertebral compression fractures: a 3-year follow-up study. Osteoporos Int. 2021;32(7):1429-39. [PMID: 33462653] doi: 10.1007/s00198-020-05816-z
3. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet. 1996;348(9041):1535-41. [PMID: 8950879] doi: 10.1016/s0140-6736(96)07088-2
4. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356(18):1809-22. [PMID: 17476007] doi: 10.1056/NEJMoa067312
5. Nakamura T, Fukunaga M, Nakano T, Kishimoto H, Ito M, Hagino H, et al. Efficacy and safety of once-yearly zoledronic acid in Japanese patients with primary osteoporosis: two-year results from a randomized placebo-controlled double-blind study (ZOledroNate treatment in Efficacy to osteoporosis; ZONE study). Osteoporosis International. 2017;28(1):389-98. [PMID: 27631091] doi: https://dx.doi.org/10.1007/s00198-016-3736-y
6. Abrahamsen B, Eiken P, Eastell R**.** Cumulative alendronate dose and the long-term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. J Clin Endocrinol Metab. 2010;95(12):5258-65. [PMID: 20843943] doi: 10.1210/jc.2010-1571
7. Black DM, Geiger EJ, Eastell R, Vittinghoff E, Li BH, Ryan DS, et al. Atypical Femur Fracture Risk versus Fragility Fracture Prevention with Bisphosphonates. New England Journal of Medicine. 2020;383(8):743-53. [PMID: doi: 10.1056/NEJMoa1916525
8. Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res. 2012;27(12):2544-50. [PMID: 22836783] doi: 10.1002/jbmr.1719
9. Hsiao FY, Huang WF, Chen YM, Wen YW, Kao YH, Chen LK, et al. Hip and subtrochanteric or diaphyseal femoral fractures in alendronate users: a 10-year, nationwide retrospective cohort study in Taiwanese women. Clin Ther. 2011;33(11):1659-67. [PMID: 22018450] doi: 10.1016/j.clinthera.2011.09.006
10. Lee YK, Byun DW, Jung SM, Kwon HY, Kim HY, Kim SH, et al. Bisphosphonates Use and Risk of Subtrochanteric and Diaphyseal Femur Fractures in Korea: Results from the National Claim Registry. Calcified Tissue International. 2019;104(3):313-9. [PMID: 30446771] doi: https://dx.doi.org/10.1007/s00223-018-0493-2
11. Lo JC, Neugebauer RS, Ettinger B, Chandra M, Hui RL, Ott SM, et al. Risk of complete atypical femur fracture with Oral bisphosphonate exposure beyond three years. BMC

Musculoskeletal Disorders. 2020;21(1):801. [PMID: 33272248] doi: https://dx.doi.org/10.1186/s12891-020-03672-w
12. Park-Wyllie LY, Mamdani MM, Juurlink DN, Hawker GA, Gunraj N, Austin PC, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. Jama. 2011;305(8):783-9. [PMID: 21343577] doi: 10.1001/jama.2011.190
13. Schilcher J, Koeppen V, Aspenberg P, Michaelsson K**.** Risk of atypical femoral fracture during and after bisphosphonate use. Acta Orthopaedica. 2015;86(1):100-7. [PMID: 25582459] doi: https://dx.doi.org/10.3109/17453674.2015.1004149
14. Schilcher J, Michaëlsson K, Aspenberg P**.** Bisphosphonate use and atypical fractures of the femoral shaft. N Engl J Med. 2011;364(18):1728-37. [PMID: 21542743] doi: 10.1056/NEJMoa1010650
15. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357(18):1799-809. [PMID: 17878149] doi: 10.1056/NEJMoa074941
16. Baillargeon J, Kuo YF, Lin YL, Wilkinson GS, Goodwin JS**.** Osteonecrosis of the jaw in older osteoporosis patients treated with intravenous bisphosphonates. Ann Pharmacother. 2011;45(10):1199-206. [PMID: 21954448] doi: 10.1345/aph.1Q239
17. Cartsos VM, Zhu S, Zavras AI**.** Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. J Am Dent Assoc. 2008;139(1):23-30. [PMID: 18167381] doi: 10.14219/jada.archive.2008.0016
18. Jung SM, Han S, Kwon HY**.** Dose-Intensity of Bisphosphonates and the Risk of Osteonecrosis of the Jaw in Osteoporosis Patients. Frontiers in Pharmacology. 2018;9:796. [PMID: 30079024] doi: https://dx.doi.org/10.3389/fphar.2018.00796
19. Kim SH, Lee YK, Kim TY, Ha YC, Jang S, Kim HY**.** Incidence of and risk for osteonecrosis of the jaw in Korean osteoporosis patients treated with bisphosphonates: A nationwide cohort-study. Bone. 2021;143:115650. [PMID: 32956854] doi: 10.1016/j.bone.2020.115650
20. Kwon JW, Park EJ, Jung SY, Sohn HS, Ryu H, Suh HS**.** A Large National Cohort Study of the Association between Bisphosphonates and Osteonecrosis of the Jaw in Patients with Osteoporosis: A Nested Case-control Study. Journal of Dental Research. 2015;94(9 Suppl):212S-9S. [PMID: 26001708] doi: https://dx.doi.org/10.1177/0022034515587862
21. Lapi F, Cipriani F, Caputi AP, Corrao G, Vaccheri A, Sturkenboom MC, et al. Assessing the risk of osteonecrosis of the jaw due to bisphosphonate therapy in the secondary prevention of osteoporotic fractures. Osteoporos Int. 2013;24(2):697-705. [PMID: 22618266] doi: 10.1007/s00198-012-2013-y
22. Tennis P, Rothman KJ, Bohn RL, Tan H, Zavras A, Laskarides C, et al. Incidence of osteonecrosis of the jaw among users of bisphosphonates with selected cancers or osteoporosis. Pharmacoepidemiol Drug Saf. 2012;21(8):810-7. [PMID: 22711458] doi: 10.1002/pds.3292
23. Wotton CJ, Green J, Brown A, Armstrong MEG, Floud S, Beral V, et al. Use of oral bisphosphonates and risk of hospital admission with osteonecrosis of the jaw: Large prospective cohort study in UK women. Bone. 2019;124:69-74. [PMID: 30959190] doi: https://dx.doi.org/10.1016/j.bone.2019.04.003

24. Bai H, Jing D, Guo A, Yin S**.** Randomized controlled trial of zoledronic acid for treatment of osteoporosis in women. J Int Med Res. 2013;41(3):697-704. [PMID: 23669294] doi: 10.1177/0300060513480917
25. Greenspan SL, Perera S, Ferchak MA, Nace DA, Resnick NM**.** Efficacy and safety of single-dose zoledronic acid for osteoporosis in frail elderly women: a randomized clinical trial. JAMA Internal Medicine. 2015;175(6):913-21. [PMID: 25867538] doi: https://dx.doi.org/10.1001/jamainternmed.2015.0747
26. Abrahamsen B, Eiken P, Brixen K**.** Atrial fibrillation in fracture patients treated with oral bisphosphonates. J Intern Med. 2009;265(5):581-92. [PMID: 19141097] doi: 10.1111/j.1365-2796.2008.02065.x
27. Bunch TJ, Anderson JL, May HT, Muhlestein JB, Horne BD, Crandall BG, et al. Relation of bisphosphonate therapies and risk of developing atrial fibrillation. Am J Cardiol. 2009;103(6):824-8. [PMID: 19268739] doi: 10.1016/j.amjcard.2008.11.037
28. Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM**.** Use of alendronate and risk of incident atrial fibrillation in women. Arch Intern Med. 2008;168(8):826-31. [PMID: 18443257] doi: 10.1001/archinte.168.8.826
29. Kirchmayer U, Sorge C, Sultana J, Lapi F, Onder G, Agabiti N, et al. Bisphosphonates and cardiovascular risk in elderly patients with previous cardiovascular disease: a population-based nested case-control study in Italy. Therapeutic Advances in Drug Safety. 2019;10:2042098619838138. [PMID: 31057787] doi: https://dx.doi.org/10.1177/2042098619838138
30. Rodriguez AJ, Ernst MT, Nybo M, Prieto-Alhambra D, Ebeling PR, Hermann AP, et al. Oral Bisphosphonate use Reduces Cardiovascular Events in a Cohort of Danish Patients Referred for Bone Mineral Density. Journal of Clinical Endocrinology & Metabolism. 2020;105(10):01. [PMID: 32717068] doi: https://dx.doi.org/10.1210/clinem/dgaa481
31. Sørensen HT, Christensen S, Mehnert F, Pedersen L, Chapurlat RD, Cummings SR, et al. Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. Bmj. 2008;336(7648):813-6. [PMID: 18334527] doi: 10.1136/bmj.39507.551644.BE
32. Yang HY, Huang JH, Chiu HW, Lin YK, Hsu CY, Chen YJ**.** Vitamin D and bisphosphonates therapies for osteoporosis are associated with different risks of atrial fibrillation in women: A nationwide population-based analysis. Medicine. 2018;97(43):e12947. [PMID: 30412111] doi: https://dx.doi.org/10.1097/MD.0000000000012947
33. Nakamura T, Matsumoto T, Sugimoto T, Hosoi T, Miki T, Gorai I, et al. Clinical Trials Express: fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: denosumab fracture intervention randomized placebo controlled trial (DIRECT). Journal of Clinical Endocrinology & Metabolism. 2014;99(7):2599-607. [PMID: 24646104] doi: https://dx.doi.org/10.1210/jc.2013-4175
34. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65. [PMID: 19671655] doi: 10.1056/NEJMoa0809493
35. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. New England Journal of Medicine. 2016;375(16):1532-43. [PMID: 27641143]

36. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. New England Journal of Medicine. 2017;377(15):1417-27. [PMID: 28892457] doi: https://dx.doi.org/10.1056/NEJMoa1708322
37. Anastasilakis AD, Papapoulos SE, Polyzos SA, Appelman-Dijkstra NM, Makras P**.** Zoledronate for the Prevention of Bone Loss in Women Discontinuing Denosumab Treatment. A Prospective 2-Year Clinical Trial. Journal of Bone & Mineral Research. 2019;34(12):2220-8. [PMID: 31433518] doi: https://dx.doi.org/10.1002/jbmr.3853
38. Kim Y, Tian Y, Yang J, Huser V, Jin P, Lambert CG, et al. Comparative safety and effectiveness of alendronate versus raloxifene in women with osteoporosis. Scientific Reports. 2020;10(1):11115. [PMID: 32632237] doi: https://dx.doi.org/10.1038/s41598-020-68037-8
39. Chiu WY, Chien JY, Yang WS, Juang JM, Lee JJ, Tsai KS**.** The risk of osteonecrosis of the jaws in Taiwanese osteoporotic patients treated with oral alendronate or raloxifene. Journal of Clinical Endocrinology & Metabolism. 2014;99(8):2729-35. [PMID: 24758181] doi: https://dx.doi.org/10.1210/jc.2013-4119
40. Chiu WY, Yang WS, Chien JY, Lee JJ, Tsai KS**.** The influence of alendronate and tooth extraction on the incidence of osteonecrosis of the jaw among osteoporotic subjects. PLoS ONE [Electronic Resource]. 2018;13(4):e0196419. [PMID: 29694412] doi: https://dx.doi.org/10.1371/journal.pone.0196419
41. Huang W-F, Tsai Y-W, Wen Y-W, Hsiao F-Y, Kuo KN, Tsai C-R**.** Osteoporosis treatment and atrial fibrillation: alendronate versus raloxifene. Menopause (New York, N.Y.). 2010;17(1):57-63. [PMID: 19680161] doi: 10.1097/gme.0b013e3181b34749
42. Lu PY, Hsieh CF, Tsai YW, Huang WF**.** Alendronate and raloxifene use related to cardiovascular diseases: differentiation by different dosing regimens of alendronate. Clin Ther. 2011;33(9):1173-9. [PMID: 21849210] doi: 10.1016/j.clinthera.2011.07.012
43. Kim SY, Schneeweiss S, Katz JN, Levin R, Solomon DH**.** Oral bisphosphonates and risk of subtrochanteric or diaphyseal femur fractures in a population-based cohort. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2011;26(5):993-1001. [PMID: 21542002] doi: 10.1002/jbmr.288
44. D'Silva KM, Cromer SJ, Yu EW, Fischer M, Kim SC**.** Risk of Incident Atrial Fibrillation With Zoledronic Acid Versus Denosumab: A Propensity Score-Matched Cohort Study. Journal of Bone & Mineral Research. 2020;02:02. [PMID: 33137852] doi: https://dx.doi.org/10.1002/jbmr.4174
45. Rhee CW, Lee J, Oh S, Choi NK, Park BJ**.** Use of bisphosphonate and risk of atrial fibrillation in older women with osteoporosis. Osteoporos Int. 2012;23(1):247-54. [PMID: 21431993] doi: 10.1007/s00198-011-1608-z
46. Ringe JD, Dorst A, Faber H, Ibach K**.** Alendronate treatment of established primary osteoporosis in men: 3-year results of a prospective, comparative, two-arm study. Rheumatol Int. 2004;24(2):110-3. [PMID: 13680141] doi: 10.1007/s00296-003-0388-y
47. Boonen S, Reginster JY, Kaufman JM, Lippuner K, Zanchetta J, Langdahl B, et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. N Engl J Med. 2012;367(18):1714-23. [PMID: 23113482] doi: 10.1056/NEJMoa1204061

48. Boonen S, Orwoll E, Magaziner J, Colón-Emeric CS, Adachi JD, Bucci-Rechtweg C, et al. Once-yearly zoledronic acid in older men compared with women with recent hip fracture. J Am Geriatr Soc. 2011;59(11):2084-90. [PMID: 22091563] doi: 10.1111/j.1532-5415.2011.03666.x
49. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD**.** Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. J Bone Miner Res. 2009;24(4):719-25. [PMID: 19049326] doi: 10.1359/jbmr.081214
50. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med. 2000;343(9):604-10. [PMID: 10979796] doi: 10.1056/NEJM200008313430902
51. Ayers C, Kansagara D, Lazur B, Fu R, Kwon A, Harrod C**.** Effectiveness and Safety of Treatments to Prevent Fractures in People With Low Bone Mass or Primary Osteoporosis : A Living Systematic Review and Network Meta-analysis for the American College of Physicians. Ann Intern Med. 2023. [PMID: 36592455] doi: 10.7326/M22-0684
52. Barrionuevo P, Gionfriddo MR, Castaneda-Guarderas A, Zeballos-Palacios C, Bora P, Mohammed K, et al. Women's Values and Preferences Regarding Osteoporosis Treatments: A Systematic Review. The Journal of Clinical Endocrinology & Metabolism. 2019;104(5):1631-6. [PMID: 30907968] doi: 10.1210/jc.2019-00193
53. Morizio P, Burkhart JI, Ozawa S**.** Denosumab: A Unique Perspective on Adherence and Cost-effectiveness Compared With Oral Bisphosphonates in Osteoporosis Patients. Annals of Pharmacotherapy. 2018;52(10):1031-41. [PMID: 29616561] doi: https://dx.doi.org/10.1177/1060028018768808
54. Willems D, Javaid MK, Pinedo-Villanueva R, Libanati C, Yehoshua A, Charokopou M**.** Importance of Time Point-Specific Indirect Treatment Comparisons of Osteoporosis Treatments: A Systematic Literature Review and Network Meta-Analyses. Clin Ther. 2022;44(1):81-97. [PMID: 35058055] doi: 10.1016/j.clinthera.2021.11.015
55. Lee SB, Park Y, Kim DW, Kwon JW, Ha JW, Yang JH, et al. Association between mortality risk and the number, location, and sequence of subsequent fractures in the elderly. Osteoporosis International. 2021;32(2):233-41. [PMID: doi: 10.1007/s00198-020-05602-x
56. Rizkallah M, Bachour F, Khoury ME, Sebaaly A, Finianos B, Hage RE, et al. Comparison of morbidity and mortality of hip and vertebral fragility fractures: Which one has the highest burden? Osteoporos Sarcopenia. 2020;6(3):146-50. [PMID: 33102809] doi: 10.1016/j.afos.2020.07.002
57. Nevitt MC, Ettinger B, Black DM, Stone K, Jamal SA, Ensrud K, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. Ann Intern Med. 1998;128(10):793-800. [PMID: 9599190] doi: 10.7326/0003-4819-128-10-199805150-00001
58. Hiligsmann M, Reginster JY, Tosteson ANA, Bukata SV, Saag KG, Gold DT, et al. Recommendations for the conduct of economic evaluations in osteoporosis: outcomes of an experts' consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)

and the US branch of the International Osteoporosis Foundation. Osteoporos Int. 2019;30(1):45-57. [PMID: 30382319] doi: 10.1007/s00198-018-4744-x
59. U.S. Centers for Medicare & Medicaid Services. Medicare Part D Drug Spending Dashboard & Data. Research, Statistics, Data & Systems. 2020; December(https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartD):Accessed in July 2021. [PMID: doi:
60. Albert SG, Reddy S**.** Clinical Evaluation of Cost Efficacy of Drugs for Treatment of Osteoporosis: A Meta-Analysis. Endocrine Practice. 2017;23(7):841-56. [PMID: 28448754] doi: https://dx.doi.org/10.4158/EP161678.RA
61. Davis S, Martyn-St James M, Sanderson J, Stevens J, Goka E, Rawdin A, et al. A systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures. Health Technology Assessment (Winchester, England). 2016;20(78):1-406. [PMID: 27801641]
62. Silverman S, Agodoa I, Kruse M, Parthan A, Orwoll E**.** Denosumab for Elderly Men with Osteoporosis: A Cost-Effectiveness Analysis from the US Payer Perspective. Journal of Osteoporosis. 2015;2015:1-9. [PMID: 26783494] doi: 10.1155/2015/627631
63. Li N, Cornelissen D, Silverman S, Pinto D, Si L, Kremer I, et al. An Updated Systematic Review of Cost-Effectiveness Analyses of Drugs for Osteoporosis. Pharmacoeconomics. 2021;39(2):181-209. [PMID: 33026634] doi: 10.1007/s40273-020-00965-9
64. McClung MR, Boonen S, Törring O, Roux C, Rizzoli R, Bone HG, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. J Bone Miner Res. 2012;27(1):211-8. [PMID: 21976367] doi: 10.1002/jbmr.536
65. Qaseem A, Forciea MA, McLean RM, Denberg TD**.** Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017;166(11):818-39. [PMID: 28492856] doi: 10.7326/m15-1361
66. Cosman F, Crittenden DB, Ferrari S, Lewiecki EM, Jaller-Raad J, Zerbini C, et al. Romosozumab FRAME Study: A Post Hoc Analysis of the Role of Regional Background Fracture Risk on Nonvertebral Fracture Outcome. Journal of Bone & Mineral Research. 2018;33(8):1407-16. [PMID: 29750828] doi: https://dx.doi.org/10.1002/jbmr.3439
67. Nakamura T, Sugimoto T, Nakano T, Kishimoto H, Ito M, Fukunaga M, et al. Randomized Teriparatide [human parathyroid hormone (PTH) 1-34] Once-Weekly Efficacy Research (TOWER) trial for examining the reduction in new vertebral fractures in subjects with primary osteoporosis and high fracture risk. J Clin Endocrinol Metab. 2012;97(9):3097-106. [PMID: 22723322] doi: 10.1210/jc.2011-3479
68. Fujita T, Fukunaga M, Itabashi A, Tsutani K, Nakamura T**.** Once-Weekly Injection of Low-Dose Teriparatide (28.2 mug) Reduced the Risk of Vertebral Fracture in Patients with Primary Osteoporosis. Calcified Tissue International. 2014;94(2):170-5. [PMID: 23963633] doi: https://dx.doi.org/10.1007/s00223-013-9777-8
69. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal

women with osteoporosis. N Engl J Med. 2001;344(19):1434-41. [PMID: 11346808] doi: 10.1056/nejm200105103441904
70. Al-Saleh Y, Al-Daghri NM, Sabico S, Alessa T, Al Emadi S, Alawadi F, et al. Diagnosis and management of osteoporosis in postmenopausal women in Gulf Cooperation Council (GCC) countries: consensus statement of the GCC countries' osteoporosis societies under the auspices of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Arch Osteoporos. 2020;15(1):109. [PMID: 32700153] doi: 10.1007/s11657-020-00778-5
71. Sanchez-Rodriguez D, Bergmann P, Body JJ, Cavalier E, Gielen E, Goemaere S, et al. The Belgian Bone Club 2020 guidelines for the management of osteoporosis in postmenopausal women. Maturitas. 2020;139:69-89. [PMID: 32747044] doi: 10.1016/j.maturitas.2020.05.006
72. Kanis JA, Johansson H, Harvey NC, Lorentzon M, Liu E, Vandenput L, et al. An assessment of intervention thresholds for very high fracture risk applied to the NOGG guidelines : A report for the National Osteoporosis Guideline Group (NOGG). Osteoporos Int. 2021;32(10):1951-60. [PMID: 33813622] doi: 10.1007/s00198-021-05942-2
73. Davis S, Simpson E, Hamilton J, James MM, Rawdin A, Wong R, et al. Denosumab, raloxifene, romosozumab and teriparatide to prevent osteoporotic fragility fractures: a systematic review and economic evaluation. Health Technology Assessment (Winchester, England). 2020;24(29):1-314. [PMID: 32588816] doi: https://dx.doi.org/10.3310/hta24290
74. McClung MR, Brown JP, Diez-Perez A, Resch H, Caminis J, Meisner P, et al. Effects of 24 Months of Treatment With Romosozumab Followed by 12 Months of Denosumab or Placebo in Postmenopausal Women With Low Bone Mineral Density: A Randomized, Double-Blind, Phase 2, Parallel Group Study. Journal of Bone and Mineral Research. 2018;33(8):1397-406. [PMID: 29694685] doi: 10.1002/jbmr.3452
75. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015;386(9999):1147-55. [PMID: 26144908] doi: 10.1016/s0140-6736(15)61120-5
76. Marketed by: Lilly USA L**.** FORTEO (teriparatide injection). Drug label approved by the U.S. Food and Drug Administration. 2002, 2021;Initial U.S. Approval: 1987(https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021318s053lbl.pdf).
77. Hagino H, Sugimoto T, Tanaka S, Sasaki K, Sone T, Nakamura T, et al. A randomized, controlled trial of once-weekly teriparatide injection versus alendronate in patients at high risk of osteoporotic fracture: primary results of the Japanese Osteoporosis Intervention Trial-05. Osteoporos Int. 2021;32(11):2301-11. [PMID: 34002252] doi: 10.1007/s00198-021-05996-2
78. Amgen Inc. EVENITY™ (romosozumab-aqqg) (insert). FDA drug label. 2019;https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761062Orig1s000Lbl.pdf.
79. Miller SA, St Onge EL, Whalen KL**.** Romosozumab: A Novel Agent in the Treatment for Postmenopausal Osteoporosis. J Pharm Technol. 2021;37(1):45-52. [PMID: 34752536] doi: 10.1177/8755122520967632

80. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2012;27(2):243-54. [PMID: 22161728] doi: 10.1002/jbmr.1494
81. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. Jama. 2006;296(24):2927-38. [PMID: 17190893] doi: 10.1001/jama.296.24.2927
82. Black DM, Reid IR, Cauley JA, Cosman F, Leung PC, Lakatos P, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). Journal of Bone & Mineral Research. 2015;30(5):934-44. [PMID: 25545380] doi: https://dx.doi.org/10.1002/jbmr.2442
83. Zhou J, Liu B, Qin MZ, Liu JP**.** Fall Prevention and Anti-Osteoporosis in Osteopenia Patients of 80 Years of Age and Older: A Randomized Controlled Study. Orthopaedic Audio-Synopsis Continuing Medical Education [Sound Recording]. 2020;12(3):890-9. [PMID: 32495521] doi: https://dx.doi.org/10.1111/os.12701
84. Eastell R, Black DM, Boonen S, Adami S, Felsenberg D, Lippuner K, et al. Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density. The Journal of clinical endocrinology and metabolism. 2009;94(9):3215-25. [PMID: 19567517] doi: 10.1210/jc.2008-2765
85. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. Jama. 1999;282(14):1344-52. [PMID: 10527181] doi: 10.1001/jama.282.14.1344
86. Reid IR, Horne AM, Mihov B, Stewart A, Garratt E, Wong S, et al. Fracture Prevention with Zoledronate in Older Women with Osteopenia. New England Journal of Medicine. 2018;379(25):2407-16. [PMID: 30575489] doi: https://dx.doi.org/10.1056/NEJMoa1808082
87. Siris ES, Simon JA, Barton IP, McClung MR, Grauer A**.** Effects of risedronate on fracture risk in postmenopausal women with osteopenia. Osteoporos Int. 2008;19(5):681-6. [PMID: 17968610] doi: 10.1007/s00198-007-0493-y
88. Boonen S, Black DM, Colón-Emeric CS, Eastell R, Magaziner JS, Eriksen EF, et al. Efficacy and safety of a once-yearly intravenous zoledronic acid 5 mg for fracture prevention in elderly postmenopausal women with osteoporosis aged 75 and older. J Am Geriatr Soc. 2010;58(2):292-9. [PMID: 20070415] doi: 10.1111/j.1532-5415.2009.02673.x
89. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. JAMA. 2016;316(7):722-33. [PMID: 27533157] doi: https://dx.doi.org/10.1001/jama.2016.11136
90. McClung MR, Harvey NC, Fitzpatrick LA, Miller PD, Hattersley G, Wang Y, et al. Effects of abaloparatide on bone mineral density and risk of fracture in postmenopausal women aged 80 years or older with osteoporosis. Menopause. 2018;25(7):767-71. [PMID: 29462094] doi: https://dx.doi.org/10.1097/GME.0000000000001080

91. McClung MR, Williams GC, Hattersley G, Fitzpatrick LA, Wang Y, Miller PD**.** Geography of Fracture Incidence in Postmenopausal Women with Osteoporosis Treated with Abaloparatide. Calcified Tissue International. 2018;102(6):627-33. [PMID: 29285549] doi: https://dx.doi.org/10.1007/s00223-017-0375-z
92. Nakano T, Shiraki M, Sugimoto T, Kishimoto H, Ito M, Fukunaga M, et al. Once-weekly teriparatide reduces the risk of vertebral fracture in patients with various fracture risks: subgroup analysis of the Teriparatide Once-Weekly Efficacy Research (TOWER) trial. Journal of Bone & Mineral Metabolism. 2014;32(4):441-6. [PMID: 24213216] doi: https://dx.doi.org/10.1007/s00774-013-0505-2
93. Boonen S, Marin F, Mellstrom D, Xie L, Desaiah D, Krege JH, et al. Safety and efficacy of teriparatide in elderly women with established osteoporosis: bone anabolic therapy from a geriatric perspective. J Am Geriatr Soc. 2006;54(5):782-9. [PMID: 16696744] doi: 10.1111/j.1532-5415.2006.00695.x
94. Palacios S, Kalouche-Khalil L, Rizzoli R, Zapalowski C, Resch H, Adachi JD, et al. Treatment with denosumab reduces secondary fracture risk in women with postmenopausal osteoporosis. Climacteric. 2015;18(6):805-12. [PMID: 26029985] doi: https://dx.doi.org/10.3109/13697137.2015.1045484
95. Geusens P, Feldman R, Oates M, Thomas T, Makras P, Jakob F, et al. Romosozumab reduces incidence of new vertebral fractures across severity grades among postmenopausal women with osteoporosis. Bone. 2022;154:116209. [PMID: 34547521] doi: 10.1016/j.bone.2021.116209
96. Geusens P, Oates M, Miyauchi A, Adachi JD, Lazaretti-Castro M, Ebeling PR, et al. The Effect of 1 Year of Romosozumab on the Incidence of Clinical Vertebral Fractures in Postmenopausal Women With Osteoporosis: Results From the FRAME Study. Jbmr Plus. 2019;3(10):e10211. [PMID: 31687647] doi: https://dx.doi.org/10.1002/jbm4.10211
97. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. J Clin Endocrinol Metab. 2002;87(8):3609-17. [PMID: 12161484] doi: 10.1210/jcem.87.8.8750
98. Palacios S, Silverman SL, de Villiers TJ, Levine AB, Goemaere S, Brown JP, et al. A 7-year randomized, placebo-controlled trial assessing the long-term efficacy and safety of bazedoxifene in postmenopausal women with osteoporosis: effects on bone density and fracture. Menopause. 2015;22(8):806-13. [PMID: 25668306] doi: https://dx.doi.org/10.1097/GME.0000000000000419
99. Delong C, Preuss CV**.** Black Box Warning. StatPearls [Internet]. 2021;https://www.ncbi.nlm.nih.gov/books/NBK538521.
100. Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2018;391(10117):230-40. [PMID: 29129436] doi: https://dx.doi.org/10.1016/S0140-6736(17)32137-2
101. Geusens P, Marin F, Kendler DL, Russo LA, Zerbini CA, Minisola S, et al. Effects of Teriparatide Compared with Risedronate on the Risk of Fractures in Subgroups of Postmenopausal Women with Severe Osteoporosis: The VERO Trial. Journal of Bone &

Mineral Research. 2018;33(5):783-94. [PMID: 29329484] doi: https://dx.doi.org/10.1002/jbmr.3384
102. Reid IR, Horne AM, Mihov B, Stewart A, Garratt E, Wiessing KR, et al. Anti-fracture efficacy of zoledronate in subgroups of osteopenic postmenopausal women: secondary analysis of a randomized controlled trial. Journal of Internal Medicine. 2019;286(2):221-9. [PMID: 30887607] doi: https://dx.doi.org/10.1111/joim.12901
103. Ferrari S, Eastell R, Napoli N, Schwartz A, Hofbauer LC, Chines A, et al. Denosumab in postmenopausal women with osteoporosis and diabetes: Subgroup analysis of FREEDOM and FREEDOM extension. Bone. 2020;134:115268. [PMID: 32058020] doi: https://dx.doi.org/10.1016/j.bone.2020.115268
104. Morii H, Ohashi Y, Taketani Y, Fukunaga M, Nakamura T, Itabashi A, et al. Effect of raloxifene on bone mineral density and biochemical markers of bone turnover in Japanese postmenopausal women with osteoporosis: results from a randomized placebo-controlled trial. Osteoporos Int. 2003;14(10):793-800. [PMID: 12955333] doi: 10.1007/s00198-003-1424-1
105. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. Jama. 1998;280(24):2077-82. [PMID: 9875874] doi: 10.1001/jama.280.24.2077
106. Nakamura T, Nakano T, Ito M, Hagino H, Hashimoto J, Tobinai M, et al. Clinical efficacy on fracture risk and safety of 0.5 mg or 1 mg/month intravenous ibandronate versus 2.5 mg/day oral risedronate in patients with primary osteoporosis. Calcif Tissue Int. 2013;93(2):137-46. [PMID: 23644930] doi: 10.1007/s00223-013-9734-6
107. Chesnut CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of Oral Ibandronate Administered Daily or Intermittently on Fracture Risk in Postmenopausal Osteoporosis. Journal of Bone and Mineral Research. 2004;19(8):1241-9. [PMID: doi: 10.1359/jbmr.040325
108. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int. 2000;11(1):83-91. [PMID: 10663363] doi: 10.1007/s001980050010
109. Silverman SL, Christiansen C, Genant HK, Vukicevic S, Zanchetta JR, de Villiers TJ, et al. Efficacy of Bazedoxifene in Reducing New Vertebral Fracture Risk in Postmenopausal Women With Osteoporosis: Results From a 3-Year, Randomized, Placebo-, and Active-Controlled Clinical Trial. Journal of Bone and Mineral Research. 2008;23(12):1923-34. [PMID: 18665787] doi: https://doi.org/10.1359/jbmr.080710
110. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Jama. 1999;282(7):637-45. [PMID: 10517716] doi: 10.1001/jama.282.7.637
111. Qaseem A, Kansagara D, Lin JS, Mustafa RA, Wilt TJ, Clinical Guidelines Committee of the American College of P, et al. The Development of Clinical Guidelines and Guidance

Statements by the Clinical Guidelines Committee of the American College of Physicians: Update of Methods. Ann Intern Med. 2019;170(12):863-70. [PMID: 31181568] doi: 10.7326/M18-3290
112. Qaseem A, Wilt TJ, Clinical Guidelines Committee of the American College of P, Forciea MA, Kansagara D, Crandall CJ, et al. Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2019;171(5):354-61. [PMID: 31426089] doi: 10.7326/M18-3279
113. Ehrenstein V, Heide-Jørgensen U, Schiødt M, Akre O, Herlofson BB, Hansen S, et al. Osteonecrosis of the jaw among patients with cancer treated with denosumab or zoledronic acid: Results of a regulator-mandated cohort postauthorization safety study in Denmark, Norway, and Sweden. Cancer. 2021;127(21):4050-8. [PMID: doi: https://doi.org/10.1002/cncr.33802
114. ClinicalTrials.gov 2015; Accessed at https://clinicaltrials.gov/ct2/show/NCT02589600 on November 9, 2021.
115. ClinicalTrials.gov 2017; Accessed at https://clinicaltrials.gov/ct2/show/NCT03293108 on November 11, 2021.
116. ClinicalTrials.gov 2019; Accessed at https://clinicaltrials.gov/ct2/show/NCT03868033 on November 12, 2021.
117. ClinicalTrials.gov 2020; Accessed at https://clinicaltrials.gov/ct2/show/NCT04591275 on November 12, 2021.
118. ClinicalTrials.gov 2021; Accessed at https://clinicaltrials.gov/ct2/show/NCT04719572 on November 12, 2021.
119. ClinicalTrials.gov 2021; Accessed at https://clinicaltrials.gov/ct2/show/NCT04729621 on November 12, 2021.
120. ClinicalTrials.gov 2021; Accessed at https://clinicaltrials.gov/ct2/show/NCT05058443 on November 12, 2021.
121. ClinicalTrials.gov 2021; Accessed at https://clinicaltrials.gov/ct2/show/NCT05065164 on November 12, 2021.
122. ClinicalTrials.gov 2021; Accessed at https://clinicaltrials.gov/ct2/show/NCT05087030 on November 12, 2021.
123. ClinicalTrials.gov 2011; Accessed at https://clinicaltrials.gov/ct2/show/NCT01416194 on November 9, 2021.
124. ClinicalTrials.gov 2013; Accessed at https://clinicaltrials.gov/ct2/show/NCT01967160 on November 9, 2021.
125. ClinicalTrials.gov 2014; Accessed at https://clinicaltrials.gov/ct2/show/NCT02304887 on November 9, 2021.
126. ClinicalTrials.gov 2015; Accessed at https://clinicaltrials.gov/ct2/show/NCT02520362 on November 9, 2021.
127. ClinicalTrials.gov 2021; Accessed at https://clinicaltrials.gov/ct2/show/NCT04974723 on November 12, 2021.
128. ClinicalTrials.gov 2021; Accessed at https://clinicaltrials.gov/ct2/show/NCT04736693 on November 12, 2021.

129. ClinicalTrials.gov 2021; Accessed at https://clinicaltrials.gov/ct2/show/NCT04879420 on November 12, 2021.