Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value

Draft Evidence Report

May 5, 2017

Prepared for

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit:
https://icer-review.org/material/osteoporosis-stakeholder-list/

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List of Acronyms Used in this Report

ACE	American College of Endocrinology
AACE	American Academy of Clinical Endocrinologists
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
ASBMR	American Society for Bone and Mineral Research
BSCA	Blue Shield of California
BMD	Bone mineral density
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CrI	Credible interval
DCHS	Department of Health Care Services
FDA	United States Food and Drug Administration
FRAX	Fracture Risk Assessment Tool
GDP	Gross domestic product
HR	Hazard ratio
IV	Intravenous
NAMS	North American Menopause Society
NMA	Network meta-analysis
NOF	National Osteoporosis Foundation
PSA	Probabilistic sensitivity analysis
PTH	Parathyroid hormone
QALY	Quality-adjusted life-year
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
UHC	United Healthcare
US	United States
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

An executive summary will be included in the revised Evidence Report, which will be released on or about June 16, 2017.

1. Background

1.1 Introduction

Background

Osteoporosis, the weakening of the bones through loss of bone mineral content and a decrease in bone quality, is a common disease of aging that is estimated to affect approximately 10 million Americans (based on bone mineral density [BMD] measurements; this does not take into account additional people who have demonstrated osteoporosis as a result of having a fragility fracture.[1] Approximately half of women and one quarter of men will experience at least one fracture due to osteoporosis during their lifetimes.[2] Experts estimate that there are approximately two million osteoporotic fractures each year, which results in $19 billion in related costs.[3] By 2025, these figures are predicted to grow to approximately three million fractures and $25 billion in costs annually as the population of older Americans increases.[3]

The goal of treatment is to prevent the fragility fractures associated with osteoporosis: most commonly hip, spine, and wrist fractures. There are two emerging anabolic (i.e., bone-building) therapies for osteoporosis: abaloparatide (Tymlos™, Radius Health, Inc.) and romosozumab (Amgen, Inc. and UCB, Inc.); romosozumab also decreases bone resorption.[4] The only other FDA-approved anabolic agent is teriparatide (Forteo®, Eli Lilly and Co.), which acts through a similar mechanism to abaloparatide. All other agents approved by the United States Food and Drug Administration (FDA) approved agents for osteoporosis are anti-resorptive (i.e., they decrease the breakdown of bone). This assessment will focus on these three anabolic agents because two of the agents are new and expected to be more effective and more expensive than generic bisphosphonates, which are the standard first-line therapy for most patients. The three drugs listed above are delivered via subcutaneous injection.

Scope of the Assessment

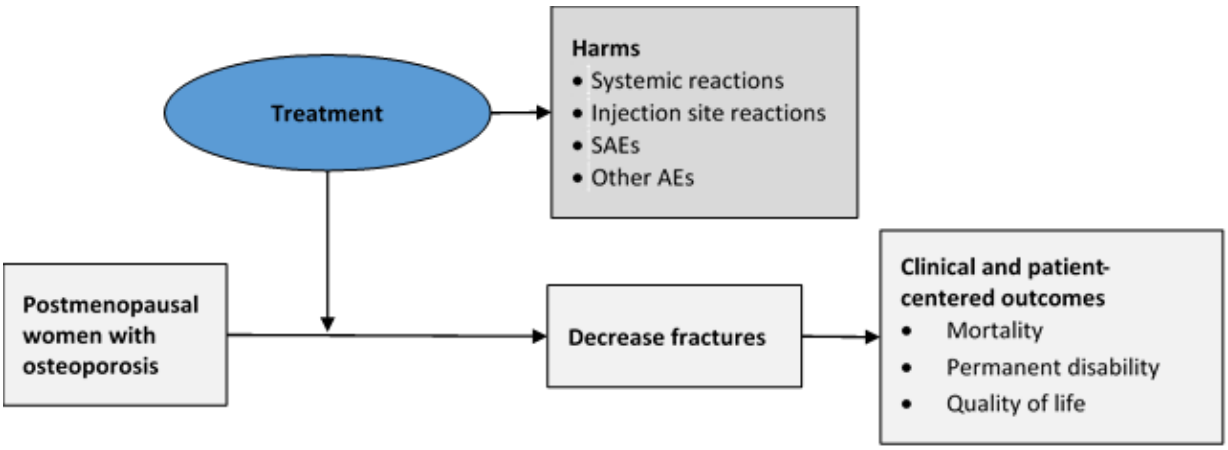
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials.

There was only one head-to-head study of these interventions with fracture outcomes,[5] so we included placebo-controlled studies and derived indirect comparisons from a network meta-analysis.

Analytic Framework

The general analytic framework for assessment of therapies for osteoporosis is depicted in Figure 1.

Figure 1. Analytic Framework: Anabolic Therapies for Osteoporosis



AE: adverse event, SAE: serious adverse event

Populations

The population for the review was postmenopausal women with an indication for treatment to prevent osteoporotic fractures, with a focus on high risk individuals such as those with a prior fragility fracture and a T-score less than -2.5. The primary focus in on women who have not received prior treatment for osteoporosis.

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Abaloparatide (Tymlos™, Radius Health, Inc.)
- Teriparatide (Forteo®, Eli Lilly and Co.)
- Romosozumab (Amgen, Inc. and UCB, Inc.)

Comparators

We compared the agents to each other, to no therapy, and to the intravenous (IV) bisphosphonate zoledronic acid. We selected zoledronic acid as the key bisphosphonate comparator because several osteoporosis guidelines recommend it for individuals at high risk for fracture and because multiple stakeholders recommended it as the most appropriate comparator. Comparing the agents

to zoledronic acid allowed us to evaluate the relative incremental benefits and harms of these agents when used first line in patients at high risk for fragility fractures.

Outcomes

The primary goal of treatment is to prevent fractures. The most important fracture to prevent is hip fracture because of the associated morbidity and mortality, but these fractures are relatively uncommon. Next in importance are clinical vertebral fractures, which are compression fractures of the spine that cause pain. Finally, non-vertebral fragility fractures were assessed. Changes in BMD, bone turnover markers, and radiographic vertebral fractures will be considered as surrogate outcomes.

Where possible we reported the absolute risk reduction and number needed to treat in addition to the relative risk reduction for the treatment comparisons.

<u>Clinical Outcomes</u>
Hip fractures
All fragility fractures
Clinical vertebral fractures
Living independently
Mobility
Pain
Ability to attend to activities of daily living
Quality of life

<u>Key harms</u>
Atypical femoral fractures
Osteonecrosis of the jaw
Osteosarcoma
Significant adverse events
Adverse events leading to discontinuation
Injection site reactions
Hypocalcemia/Hypercalcemia

<u>Non-clinical Outcomes</u>
Bone mineral density
Bone turnover markers
Radiographic vertebral fractures

Timing

Evidence on intervention effectiveness was derived from studies of at least one year's duration.

Settings

All relevant settings were considered, with a focus on outpatient settings.

2. The Topic in Context

Osteoporotic fractures occur most commonly in older, white women. Of the estimated 2 million fractures occurring in 2005 in the United States, 71% occurred in women and only 14% occurred in non-white Americans.[3] For example, the age-standardized rates of hip fracture in 2008-2009 were 58% lower in black women than white women, 49% lower in Asian women, and 39% lower in Hispanic women.[6]

Osteoporosis is diagnosed primarily through measurement of bone density at the hip and lumbar spine. Bone density is reported as the number of standard deviations from the bone mass of a young, healthy woman. This is called the T-score. Since humans achieve peak bone mass around the age of 30, the T-score is usually negative. A T-score of -1 or higher is considered normal; a T-score between -1 and -2.5 is considered low bone mass or osteopenia; and a T-score less than -2.5 is considered osteoporosis. The average T-score for a 75-year old white woman is -2.5, so about half of women ages 75 and older have osteoporosis. Osteoporosis is also diagnosed when an individual experiences a fragility fracture in a location associated with osteoporosis. A fragility fracture is a low-energy fracture that would not normally be expected to result in a broken bone, such as a fall from standing height or less. The most common fractures associated with osteoporosis are vertebral (27%), wrist (19%), hip (14%), and pelvic (7%).[3]

The US Preventive Services Task Force (USPSTF) recommends screening average-risk women with a bone density measurement at age 65, and screening younger women who have risk factors that give them the risk of a 65-year old woman. However, screening rates are only about 26% for women 65 to 74 years of age.[7]

Common risk factors for osteoporosis include older age, female sex, prior fractures, smoking, low body mass index, hyperthyroidism, excessive alcohol intake, malabsorption, and some medications (corticosteroids, seizure medications). Many other less common medical conditions and medications impact the risk of fracture.

Several organizations have treatment guidelines for osteoporosis including the National Osteoporosis Foundation (NOF), the American Society for Bone and Mineral Research (ASBMR), the American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology (ACE), and the North American Menopause Society (NAMS). There is general agreement that treatment is indicated for patients over age 50 who have experienced a hip or vertebral fracture or have a bone density T-score less than or equal to -2.5. Treatment is also indicated for patients with a T-score from -1 to -2.5 and a 10-year probability of hip fracture ≥ 3% or a 10-year probability of a major osteoporotic fracture ≥ 20%. For most patients, first-line therapy is to ensure adequate vitamin D and calcium intake, weight bearing exercise, and an oral medication from the

bisphosphonate class of drugs. If patients are unable to tolerate oral bisphosphonates or compliance cannot be ascertained, then IV bisphosphonates are generally recommended. Bone is constantly broken down (resorption) and rebuilt; bisphosphonates work by decreasing bone resorption. There are several other drugs approved for osteoporosis that also decrease bone resorption (estrogen, calcitonin, raloxifene, denosumab). They are not considered first-line therapies because of side effects or less evidence of efficacy.

Osteoporotic fractures can lead to pain, disability, and death. Even vertebral fractures that did not come to clinical attention pain may result in loss of height and pronounced curving of the spine (kyphosis) that interfere with activities and make breathing difficult. Patients have become increasingly concerned about two adverse events associated with use of bisphosphonate therapy: osteonecrosis of the jaw and atypical femoral fractures. These concerns may partially explain the 50% decrease in the use of bisphosphonate therapy from 2008 to 2012 in the US.[8] Practitioners and clinical societies have noted that rates of osteonecrosis of the jaw and atypical femoral fractures in treated patients are much lower than rates of hip fractures in untreated individuals, and that the overall benefit of treatment is far greater than the harm.

Adherence with bisphosphonate therapy is a major concern. The oral bisphosphonates must be taken with water on an empty stomach in the morning and then the patient needs to remain upright for at least 30 minutes without consuming any additional food or medications. Observational studies in the real world report estimate that only 45% of patients remain adherent with oral bisphosphonate therapy one year after the initial prescription and only 30% after two years.[9] The long-acting bisphosphonate, zoledronic acid, which requires only one IV infusion each year may have greater adherence, but some studies report greater than 50% discontinuation of therapy with zoledronic acid by two years.[10] This appears to be a problem across classes of parenteral agents for osteoporosis with discontinuation rates at one year of 49% for denosumab (a fully humanized monoclonal antibody against the RANKL cytokine with anti-resorptive effects), 59% for zoledronic acid, and 67% for teriparatide.[10]

Given the poor adherence to currently available therapies, new therapies are needed. Individuals on currently-approved therapy continue to experience fragility fractures, so many may benefit from drugs with greater efficacy and acceptable side-effect profiles.

Anabolic or Bone-Building Agents

Parathyroid Hormone (PTH) Analog Drugs

Teriparatide was the first drug approved by the FDA for the treatment of osteoporosis that works primarily by increasing bone formation rather than decreasing bone resorption. It is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture. In the label, high risk for fracture is defined as a history of osteoporotic fracture, or multiple risk

factors for fracture, or prior unsuccessful treatment with or intolerance to previous osteoporosis therapy, based upon physician assessment.[11] Teriparatide requires a daily injection of 20 mcg under the skin and the drug must be kept refrigerated. In rat studies, teriparatide caused bone tumors (osteosarcomas); however, these have not been observed in humans. Due to concerns that prolonged use could cause osteosarcomas, teriparatide is only used for two years.

Abaloparatide is a new PTH analog, approved by the FDA on 4/28/17, and is similar to teriparatide.[12] It is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture; high fracture risk is defined using the same terms as in the teriparatide label.[13] Abaloparatide requires a daily injection of 20 mcg under the skin, but does not require refrigeration after the first dose.

Anti-Sclerostin Antibodies

Romosozumab is a monoclonal antibody directed at the protein sclerostin. Sclerostin decreases bone formation, and by blocking sclerostin function, romosozumab increases bone formation and thus builds bone. Romosozumab also appears to have anti-resorptive effects. It is given by subcutaneous injection once monthly and requires refrigeration. It has not yet been approved by the FDA, but a decision is expected on 7/19/2017.[14]

Definitions

Table 1. Categories of Bone Density

T-score	Category
0 to -1.0	Normal bone mass
-1 to -2.5	Low bone mass
<-2.5	Osteoporosis

Fragility fractures: Fractures caused by forces that would not normally cause a fracture, usually defined as a fall from a standing height or less.

Vertebral fractures: The majority of vertebral fractures are not diagnosed. As required for FDA approval, the primary outcome in most of the pivotal trials is new vertebral fractures identified by a radiographic assessment of paired x-rays of the spine obtained before randomization and at the end of the trial. These are known as **morphometric vertebral fractures**. The subset of morphometric fractures that are diagnosed clinically are called **clinical vertebral fractures**.

Table 2. Grading of Vertebral Fractures

Decrease in Height	Category
20% to 25%	Mild (Grade 1)
26% to 40%	Moderate (Grade 2)
>40%	Severe (Grade 3)

Major osteoporotic fracture: A major osteoporotic fracture is a fracture of the proximal humerus, the wrist, the hip, or a clinical vertebral fracture.

Insights Gained from Discussions with Patients and Patient Groups

In the NOF's Bone Health Index Survey in 2016, patients ranked loss of independence (42%) and lost mobility (25%) as their top two concerns.[15] The primary concern among caregivers of patients with osteoporosis was that they would not be able to manage the care of their loved one (50%). Other notable findings included 60% of patients who had sustained a fracture reported not being referred for a bone density test, and fewer than half (47%) were prescribed a medication for osteoporosis. Among those prescribed a medication, 38% said that they never took it, primarily because of fears about side effects (79%). More than half of patients (51%) who started a medication stopped taking it because of side effects (53%) or concerns about the risk for side effects (38%).

Patient groups told us that clinical trials rarely report the outcomes that are most meaningful to patients. These include living independently, the ability to perform the activities of daily living, social engagement, quality of life, reduced fear and anxiety about the disease and treatment, and safety from adverse drug effects. Other outcomes include pain, mobility, depression, and caregiver burden.

The details of taking the medication are also important. Medications that require refrigeration (teriparatide, romosozumab) may be particularly burdensome. Many patients have a fear of needles, which is another barrier to adherence.

There are also insurance barriers to treatment. One patient noted that "health care today is so confusing with copay and coinsurance that I never know what is the right way to go." Patients also note that insurance often requires that they fail an oral therapy before authorizing an injectable therapy. This adds administrative burden on clinicians, and extra office visits for patients.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

To understand the insurance landscape for osteoporosis treatments, we reviewed publicly-available coverage policies from the Centers for Medicare and Medicaid Services (CMS); California Department of Health Care Services (DHCS); Medicare Part D Plans offered by major private national and California-based insurers (Aetna, Anthem, Cigna, Humana, United Healthcare [UHC], Health Net and Blue Shield of California [BSCA]); and silver-tier Covered California plans offered in both Northern and Southern California (Anthem, Health Net, Kaiser Permanente, and BSCA). As abaloparatide and romosozumab have yet to be approved by the FDA, we focused on policies pertaining to teriparatide, oral alendronate, and zoledronic acid.

We were unable to identify any CMS National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs) relevant to California related to the use of bisphosphonates or teriparatide. California DHCS listed both alendronate and zoledronic acid, but not teriparatide, on its contract drug list.[16]

Teriparatide may be covered under Medicare Part B (when administered in a hospital setting or by a home health aide) or Part D (when self-administered). When covered under Part D, each of the surveyed Medicare Part D plans listed teriparatide at the specialty formulary tier, indicating that patients would be subject to higher out-of-pocket costs (Table 3).[17-23] Four of seven plans (Anthem, Aetna, UHC, BSCA) required T-scores of -2.5 or lower. However, each of these payers also covered the drug for patients with prior fragility fractures and/or prior treatment failure, contraindication, or intolerance to another osteoporosis therapy, most frequently an oral bisphosphonate. Only two payers defined treatment failure in their policies; BSCA listed a T-score that remains ≤ -2.5 with or without a low-impact fracture while on bisphosphonate treatment, while Cigna listed a "significant" decrease in BMD after one year of treatment or a new fracture while on bisphosphonate treatment. Cigna and BSCA also required prior therapy with denosumab.[24-27] Two payers, Cigna and UHC, covered teriparatide with no additional requirements for patients with T-scores of -3.5 or lower.[28] Humana did not require a T-score, only that patients demonstrate the failure of or contraindication/intolerance to one oral bisphosphonate.[29] Only one payer, Health Net, did not utilize step therapy or prior authorization requirements for teriparatide.

As an illustrative example, Anthem's prior authorization policy covered teriparatide for individuals with a T-score of -2.5 or lower; or a history of one or more fragility fractures at high risk for fracture; or more than three months of systemic corticosteroid use. Risk factors for fracture include a history

of fracture, sustained glucocorticoid use, advanced age, family history of osteoporosis, cigarette smoking, three or more alcoholic drinks per day, etc.; or prior unsuccessful treatment with or intolerance to at least one other osteoporosis therapy.

All of the surveyed Part D Plans covered alendronate at the lowest or second-lowest formulary tier. One payer, Anthem, included zoledronic acid at the lowest tier; five payers (Aetna, Cigna, UHC, Health Net, BSCA) listed the drug at the highest non-specialty tier (i.e., patients would be subject to greater out-of-pocket costs for zoledronic acid as compared to alendronate); and one payer (Humana) listed the drug at the specialty tier. For zoledronic acid, UHC required patients to meet one of the following criteria: 1) a T-score of lower than -2.5, 2) a recent vertebral compression fracture or fragility fracture of the hip or distal radius, or 3) a T-score from -1 to -2.5 and a 10-year probability of hip fracture greater than 3% or a 10-year probability of major osteoporotic fracture greater than 20%. Humana required patients to attempt treatment with one oral bisphosphonate prior to zoledronic acid, and BSCA required an attempt at oral bisphosphonate therapy or a recent fragility fracture of the hip.[30-32] Although Anthem lists a prior authorization requirement for zoledronic acid, we were unable to locate any publicly-available information about its policy.

Each of the surveyed silver-tier exchange plans covered teriparatide at the specialty tier (Appendix Table B1).[21,33-36] Only Health Net required prior authorization for teriparatide, and their policy required prior unsuccessful treatment with alendronate and a diagnosis of osteoporosis, a high risk of osteoporosis, or glucocorticoid-induced osteoporosis before coverage will be authorized.[37] All four plans covered alendronate without prior authorization or step therapy requirements at the lowest or second-lowest formulary tier. Two insurers, Health Net and BSCA, did not include zoledronic acid in their formularies for silver-tier exchange plans; Anthem covered the drug at the fourth, or highest, tier; and Kaiser Permanente covered the drug at the lowest tier.

Table 3. Representative Medicare Part D Plan Coverage Policies for Teriparatide, Alendronate, and Zoledronic Acid

	Anthem	Aetna	Cigna	Humana	UHC	Health Net	BSCA
Teriparatide							
Tier	4	5	5	4	5	5	6
ST	No	No	No	Yes	No	No	No
PA	Yes	Yes	Yes	No	Yes	No	Yes
T-score	≤ -2.5	≤ -2.5	≤ -3.5*	None	≤ -3.5* or ≤ -2.5†	None	≤ -2.5
Tx Failure	1 oral bisphosphonate	1 oral bisphosphonate/SERM	1 oral bisphosphonate and denosumab	1 oral bisphosphonate	1 bisphosphonate	None	1 monthly bisphosphonate and denosumab
I/C	2 oral bisphosphonates	2 oral bisphosphonates or SERMs	1 oral bisphosphonate and denosumab	2 oral bisphosphonates	1 bisphosphonate	None	1 monthly bisphosphonate and denosumab
Alendronate							
Tier	1	1	2	2	1	1	2
ST	No	No	No	No	No	No	No
PA	No	No	No	No	No	No	No
Zoledronic Acid							
Tier	1	4	4	4	4	4	5
ST	No	No	No	No	No	No	No
PA	Yes	No	Yes‡	Yes	Yes‡	No	Yes
T-score	None	None	None	None	-2.5	None	None
Tx Failure	None	None	None	1 oral bisphosphonate	None	None	1 oral bisphosphonate§
I/C	None	None	None	1 oral bisphosphonate	None	None	1 oral bisphosphonate§

BSCA: Blue Shield of California, I/C: intolerance/contraindication, PA: prior authorization, SERM: selective estrogen receptor modulator, ST: step therapy, Tx: treatment, UHC: United Healthcare

*Individuals with a T-score of less than -3.5 do not need to meet failure/intolerance/contraindication criteria

†Also requires a prior fragility fracture or tx failure/intolerance. Coverage is authorized regardless of BMD T-score for individuals with a prior fragility fracture and bisphosphonate failure/intolerance/contraindication.

‡PA only to determine whether coverage is provided under Medicare Part B or D. As an infused drug, zoledronic acid would be covered under Part D.

§Coverage is also authorized for individuals with a recent hip fragility fracture

3.2 Clinical Guidelines

To better understand the perspective of clinical specialty societies on the appropriate treatment of postmenopausal osteoporosis, we reviewed guideline statements issued by selected US and ex-US organizations. For the purposes of this report, we have focused on recommendations that are relevant to the treatment of postmenopausal women with osteoporosis and have not summarized guiding statements related to primary prevention, secondary osteoporosis, or the treatment of osteoporosis in men. All of the guidelines used terms such as "low," "moderate," "high," or "severe" risk for fracture, but did not explicitly define these levels of risk.

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), 2016[38]

The AACE/ACE guidelines, which are based upon expert opinion, recommend that all postmenopausal women over the age of 50 be screened for osteoporosis risk. Osteoporosis may be diagnosed in patients who meet one of four criteria: 1) a T-score of ≤ -2.5 in the lumbar spine, femoral neck, total hip, and/or radius; 2) a fragility fracture at any BMD T-score; 3) osteopenia (T-score of -1.0 to -2.5) and a fragility fracture of the humerus, pelvis, or distal forearm; 4) or osteopenia and a high FRAX probability of fracture. Low, moderate, and high risk categories are not conclusively defined, but risk factors include ethnicity, age, sex, body mass index (BMI), BMD, family history, long-term glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, more than three units of alcohol intake per day, smoking, and several other factors.

Pharmacologic therapy is strongly recommended for individuals who meet the above criteria; for individuals with osteopenia, treatment is indicated when the FRAX 10-year probability of major osteoporotic fracture or hip fracture is ≥ 20% or 3%, respectively. Alendronate, risedronate, zoledronic acid, and denosumab are recommended as first-line agents for most patients with osteoporosis, with oral agents (alendronate and risedronate) being recommended for individuals who are at low to moderate risk of fracture (e.g., younger postmenopausal women without prior fractures and a "moderately low" T-score). Teriparatide, zoledronic acid, and denosumab are recommended for individuals with the highest fracture risk (e.g., older women with multiple prior fractures or a very low T-score; individuals in whom oral therapy is contraindicated due to intolerance, likelihood of poor medication absorption, or difficulties with treatment adherence). Teriparatide should be followed by treatment with an antiresorptive agent to preserve bone density gains and reduction in fracture risk. Combination therapy is not recommended for the treatment or prevention of postmenopausal osteoporosis.

The AACE/ACE recommends that the use of teriparatide is limited to 2 years. Oral bisphosphonates may be used for longer periods, but the guidelines suggest "bisphosphonate holidays" may be appropriate after five years of stable treatment for individuals at low to moderate risk, and after six

to 10 years of stable treatment in patients at the highest risk. For individuals treated with zoledronic acid, treatment holidays should be considered after three annual doses for women at low to moderate risk, and after six annual doses for individuals at higher risk. Teriparatide may be used during bisphosphonate holidays for high-risk patients. The AACE/ACE guidelines note that there are no clear data on the optimal duration of a drug holiday, but suggest that the duration of treatment holidays may be longest for zoledronic acid, of moderate length with alendronate, and of shortest duration with risedronate due to each drug's bone-binding affinity. Resumption of therapy should be considered in patients who experience a fracture or substantial decline in BMD.

American Society for Bone and Mineral Research (ASBMR), 2016[39]

The ASBMR guidelines, which are based upon expert opinion, pertain to the management of osteoporosis in patients who are on long-term bisphosphonate treatment. For postmenopausal women on bisphosphonate therapy, the ASBMR recommends that physicians reassess their patients' fracture risk after five years of oral bisphosphonate treatment, or three years of intravenous bisphosphonate treatment. Physicians should consider continuing therapy or switching to an alternative agent in patients who experience a hip, spine, or multiple other osteoporotic fractures during the initial treatment period; who have an on-therapy hip BMD T-score of ≤ -2.5; or who remain at high risk for fracture based on factors including age, body mass index (BMI), or a history of major osteoporotic fracture. Postmenopausal women who meet these criteria should be considered candidates for up to 10 years of treatment with an oral bisphosphonate or six years of treatment with an IV bisphosphonate. The guidelines recommend that patients who continue treatment be re-evaluated for fracture risk every two to three years.

Patients with low to moderate risk of fracture after treatment may be considered candidates for a drug holiday of two to three years in length, and patients on a drug holiday should be reassessed for fracture risk every two to three years. Earlier reassessment should be considered for patients who experience a fracture during the drug holiday, and for individuals who are likely to experience rapid bone loss due to other factors such as treatment with glucocorticoids.

National Osteoporosis Foundation (NOF), 2014[40]

The NOF guidelines, which are based upon a cost-effectiveness analyses plus expert opinion, recommend pharmacologic treatment in women with a history of clinical or radiographic hip or vertebral fractures; in patients with a T-score of ≤ -2.5 at the femoral neck, total hip, or lumbar spine; or in patients with osteopenia (T-score between -1.0 and -2.5 at the femoral neck, total hip, or lumbar spine) and FRAX 10-year probability of major osteoporotic fracture or hip fracture of ≥ 20% or 3%, respectively. Patients with severe osteoporosis should initiate treatment with an anabolic agent, and anabolic therapy should be immediately followed by a bisphosphonate. Combination therapy with teriparatide and an anti-resorptive therapy may be considered in rare

cases, such as in patients those with very severe osteoporosis (e.g., a hip and spine fracture), and short-term combination therapy with a two anti-resorptive agents may be considered for women who experience bone loss while being treated with low-dose hormone therapy for menopausal symptoms or raloxifene for breast cancer prevention. In contrast to the AACE/ACE guidelines, the NOF recommendations do not specify which treatments (bisphosphonates or anabolic agents) are most appropriate for patients of various levels of risk.

The NOF guidelines do not recommend indefinite treatment with any agent. The guidelines note that the benefits of anabolic therapy diminish rapidly if not followed by an anti-resorptive treatment, but that the benefits of anti-resorptive therapy persist after treatment discontinuation. As such, it is appropriate to consider treatment discontinuation for patients at "modest" risk of fracture after three to five years of treatment with bisphosphonates. Patients with a high fracture risk despite treatment should continue to take bisphosphonates or an alternative therapy.

North American Menopause Society (NAMS), 2010[41]

The NAMS guidelines, which are based upon expert opinion, recommend pharmacologic treatment in postmenopausal women who have had an osteoporotic fracture of the vertebra or hip; or who have a T-score ≤ -2.5 in the lumbar spine, femoral neck, or total hip; or who have a T-score between -1.0 and -2.5 and a 10-year risk of major osteoporotic fracture or hip fracture ≥ 20% and 3%, respectively. NAMS recommends that bisphosphonates be used as first-line treatments, and that teriparatide be reserved for individuals at high risk for osteoporotic fracture.

The guidelines do not recommend an optimal duration for bisphosphonate treatment. Teriparatide may be used for a maximum of 24 months. The guidelines do not include recommendations related to treatment sequencing or combination therapy. Treatment discontinuation should be guided by individual patient characteristics, including fracture risk and response to therapy.

National Institute for Health and Care Excellence (NICE), 2017[42]

The NICE guidelines (from the United Kingdom) pertain only to the prevention of fracture in women with osteoporosis who have had a fragility fracture. Alendronate is recommended as a first-line treatment option. Risedronate and etidronate are listed as second-line treatment options for patients who cannot comply with alendronate's administration requirements or have a contraindication or intolerance to the drug. In addition, patients must meet several criteria related to age, BMD, and the presence of independent clinical risk factors (e.g., history of hip fracture in the patient's parent, more than 4 units of alcohol consumption per day, rheumatoid arthritis). For example, treatment would be recommended for a woman aged 55-59 years with a T-score of -4.0 and no independent risk factors, and for women in the same age range with a T-score of -3.5 and one independent risk factor. Strontium ranelate and raloxifene are considered third-line therapies for patients who cannot comply with administration instructions for first- or second-line treatments

or have a contraindication or intolerance to those options. Similar additional criteria related to BMD, age, and independent risk factors are also applied. The guidelines recommend teriparatide as a third-line option for women who have been unsuccessfully treated with alendronate and either risedronate or etidronate, or who have a contraindication/intolerance to the aforementioned drugs (including strontium ranelate, but not raloxifene). In addition, candidates for teriparatide should be ages 65+ with a T-score of -4.0, or ages 65+ with a T-score of ≤ -3.5 and more than two fractures, or ages 55-64 with a T-score of ≤ -4.0 and more than two fractures. Denosumab is also listed as a third-line treatment option for patients unable to appropriately administer alendronate and either risedronate or etidronate, or who have a contraindication or intolerance to those drugs.

The guidelines recommend that physicians and patients discuss cessation of bisphosphonate treatment after three years of therapy. Several factors may inform these discussion, including individual choice, fracture risk, and life expectancy.

4. Comparative Clinical Effectiveness

4.1 Overview

We abstracted data from the pivotal randomized trials of teriparatide, abaloparatide and romosozumab. We focused primarily on fracture outcomes (vertebral, hip, wrist, non-vertebral) and potential harms. Given the paucity of head-to-head trials, we performed a network meta-analysis (NMA) to generate indirect comparisons between each of the anabolic agents. We included the pivotal trial for zoledronic acid in the NMA because it is the bisphosphonate that the recent AACE/ACE guidelines recommend for patients at highest risk for fracture along with teriparatide. We did not include denosumab because it is not an anabolic agent (the primary focus of this report) and because multiple stakeholders recommended that we use zoledronic acid as the primary comparator. We expect that the other two anabolic agents will also be primarily used in patients at highest risk for fracture.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on anabolic therapies for osteoporosis followed established best methods.[43,44] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[45] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We searched MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. The search was limited to English-language studies of human subjects and focused on trials of at least one year's duration; articles indexed as guidelines, letters, editorials, narrative reviews, or news items were excluded.

The search strategies included a combination of indexing terms (MeSH terms in MEDLINE/PubMed and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix Tables A2-A4. In order to supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. We also contacted manufacturers, specialty societies, and patient advocacy organizations to ensure that we captured all of the relevant literature.

Study Selection

After the literature search and removal of duplicate citations using both online and local software tools, study selection was performed using two levels of screening, at the abstract and full-text level. Two reviewers screened the titles and abstracts of all publications identified through electronic searches per the inclusion and exclusion criteria defined by the PICOTS elements; a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. No study was excluded at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening were retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Key inclusion criteria included studies of 1) at least one year's duration that 2) reported fracture outcomes for 3) postmenopausal women with osteoporosis treated with 4) at least one of the drugs of interest (teriparatide, abaloparatide, romosozumab) compared to 5) another of the drugs of interest or placebo.

Data Extraction and Quality Assessment

For the systematic literature review, the data abstraction was performed using the following steps:

1. Two reviewers abstracted information from the full articles.
2. Abstracted data were reviewed for logic, and a random proportion of data was validated by a third investigator for additional quality assurance.

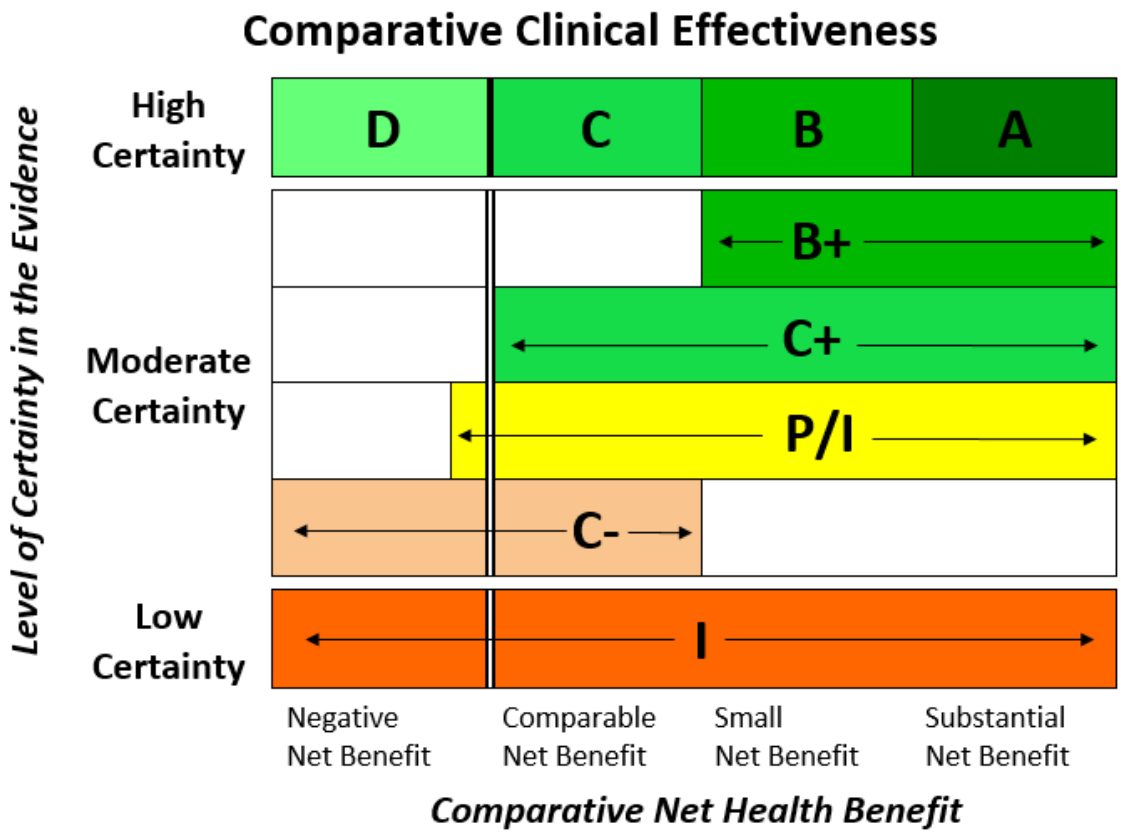
Information from the accepted studies was extracted into data extraction forms and summarized in Appendix Tables E1-E7.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (Figure 2) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[46]

Figure 2. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in Appendix Tables E5-E7, and synthesized qualitatively below.

In addition, we conducted NMAs using a mixed treatment comparison approach.[47] Quantitative analyses were conducted using WinBUGS statistical software for Bayesian analysis (MRC Biostatistics Unit, Cambridge, UK). We fit fixed treatment effect models using non-informative

normal priors. A total of 40,000 iterations each were used for both "burn-in" (for model convergence) and model (for model results) simulations.

We reviewed the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points to assess model fit under multiple alternative assumptions. The paucity of studies precluded meta-regression and extensive sensitivity analyses. We did sensitivity analyses excluding the data from the open label teriparatide arm of the ACTIVE trial.

4.3 Results

For each of the three anabolic drugs, there is only one pivotal trial. Each pivotal trial is described in detail in the key studies section below. The pivotal study of zoledronic acid is also described because it is the comparator bisphosphonate therapy in the cost-effectiveness model and we included it in the NMA that provides estimates for the reduction in fractures used in the cost model.

Study Selection

The literature search identified 788 citations (Appendix Figure A1). After reviewing the titles and abstracts, 222 full-text articles were evaluated. Three randomized trials met all inclusion and exclusion criteria.[5,48,49] Details of the studies are summarized in Appendix Tables E1-E7.

Key Studies

The Fracture Prevention Trial – Teriparatide[49]

The Fracture Prevention Trial randomized 1,085 patients to daily subcutaneous (SC) injections of teriparatide 20 mcg or identical placebo and followed them for 21 of the planned 24 months.[49] The study was terminated early to investigate concerns raised because of the development of osteosarcomas in rats during a toxicology study. No osteosarcomas developed in the human participants in this trial. The participants were women at least five years after their menopause who had at least one moderate or two mild vertebral fractures. At baseline, the mean T-score was not reported and 100% had existing vertebral fracture. The primary outcome was not specified, but was likely new morphometric vertebral fractures. New vertebral fractures occurred in 5% of women in the teriparatide group and 14% of women in the placebo group (relative risk [RR] 0.35, 95% confidence interval [CI] 0.22-0.55). Non-vertebral fragility fractures occurred in 6% of women in the teriparatide group and 10% of women in the placebo group (RR 0.47, 95% CI 0.25-0.88). Hip fractures occurred in 0.2% of women in the teriparatide group and 0.7% of women in the placebo group (RR not reported). Discontinuation of the study drug due to adverse events was identical in the two groups (6%). Dizziness (9% vs. 3%) and leg cramps (3% vs. 1%) were more common in the teriparatide group. Hypercalcemia was also more common in the teriparatide group (11% vs. 2%).

Adherence, based on returned medication, was approximately 81% for both teriparatide and placebo injections at each follow-up visit.

The ACTIVE Trial – Abaloparatide[5]

The ACTIVE trial randomized 2,463 patients to daily SC injections of abaloparatide 80 mcg, teriparatide 20 mcg or identical placebo and followed them for 18 months.[5] The teriparatide was given open label. The participants were postmenopausal women ages 49 to 86 years who had at least one moderate or two mild vertebral fractures or other fragility fractures in the past five years and bone mineral density (BMD) T-scores between -2.5 and -5.0, or women at least 65 years of age without a history of a fragility fracture with BMD T-scores between -3.0 and -5.0. At baseline, the mean T-score at the total hip was -1.9 and 24% had existing vertebral fracture. The primary outcome was the cumulative incidence of new vertebral fractures. New vertebral fractures occurred in 0.6% of women in the abaloparatide group, 0.8% of women in the teriparatide group, and 4.2% of women in the placebo group (abaloparatide hazard ratio [HR] 0.14, 95% CI 0.05-0.39; teriparatide HR 0.20, 95% CI 0.08-0.47, both vs. placebo). The HR for abaloparatide versus teriparatide was not reported for vertebral fractures. Non-vertebral fragility fractures occurred in 2.7% of women in the abaloparatide group, 3.3% of women in the teriparatide group and 4.7% of women in the placebo group (abaloparatide HR 0.57, 95% CI 0.32-1.00; teriparatide HR 0.72, 95% CI 0.42-1.22, both vs. placebo). The HR for abaloparatide versus teriparatide was 0.79 (95% CI 0.43-1.45) for nonvertebral fractures. There were no hip fractures in either the abaloparatide or teriparatide groups and 2 (0.2%) in the placebo group (HRs not reported). Discontinuation of the study drug due to adverse events was higher in the abaloparatide group (9.9% vs. teriparatide 6.8% and placebo 6.1%). However, rates of significant adverse events were similar in the three groups (9.7%, 10.0%, and 11%). Hypercalcemia was more common in the PTH analog groups (3.4% abaloparatide, 6.4% teriparatide, 0.4% placebo). Adherence, based on weekly diary recording, was greater than 90% for each of the treatment groups.

Patients in both the abaloparatide and placebo groups of the ACTIVE trial were offered an additional two years of follow-up receiving open-label oral alendronate 70 mg weekly and 92% of eligible patients agreed to participate. The six-month follow-up results reported lower rates of vertebral fractures (HR 0.13, 95% CI 0.04-0.41), non-vertebral fractures (HR 0.48, 95% CI 0.26-0.89), and major osteoporotic fractures (HR 0.42, 95% CI 0.21-0.85) for abaloparatide followed by alendronate compared to placebo followed by alendronate when analyzed from the beginning of the ACTIVE trial.[50] However, the number of new fractures in the extension trial was low in both the abaloparatide/alendronate and placebo/alendronate groups (vertebral 0 vs. 7; non-vertebral 3 vs. 7; major osteoporotic 2 vs. 4). This suggests that alendronate therapy can preserve the fracture reduction benefits of abaloparatide, but the interim results should be considered preliminary until the full two-year extension study results are published.

The FRAME Study – Romosozumab[48]

The FRAME study randomized 7,180 patients to monthly SC injections of romosozumab 210 mg or identical placebo for 12 months followed by an additional 12 months of denosumab.[48] The participants were women ages 55 to 90 years of age with BMD T-scores between -3.0 and -5.0. Mean total hip T-score was -2.5 and 18% had vertebral fractures at baseline. The co-primary outcomes were the cumulative incidence of new vertebral fractures at 12 and 24 months. At 12 months, new vertebral fractures occurred in 0.5% of women in the romosozumab group and 1.8% of women in the placebo group (RR 0.27, 95% CI 0.16-0.47). Non-vertebral fractures occurred in 1.6% of women in the romosozumab group and 2.1% of women in the placebo group (RR 0.75, 95% CI 0.53-1.05). Hip fractures occurred in 0.2% of women in the romosozumab group and 0.4% of women in the placebo group (RR 0.54, 95% CI 0.22-1.35). Effect modification was evaluated in 11 subgroups including age, history of fracture, T-score, and geographic region for new vertebral, clinical, and non-vertebral fractures. The treatment effects were consistent in all subgroups except for treatment by region interactions for clinical and non-vertebral fractures (nominal p values 0.03 and 0.04, respectively). Post-hoc analyses suggested that romosozumab may be less effective in the Latin American region, though this could be a chance finding given the multiple comparisons performed without any adjustment.

During the first 12 months, discontinuation of the study drug due to adverse events was similar in the two groups (2.9% vs. 2.6%). There were seven patients with serious possible hypersensitivity reactions in the romosozumab group. In addition, injection site reactions were more common in the romosozumab group (5.2% vs. 2.9%). Of note in such a short study, one patient in the romosozumab group had an atypical femoral fracture and one had osteonecrosis of the jaw. These events may be due to chance, but could reflect the anti-resorptive properties of romosozumab. Adherence was not reported.

After 12 months, all patients in the FRAME study received denosumab 60 mg SC every six months for an additional 12 months. The cumulative risk for the full 24-month period for new vertebral fractures (RR 0.25, 95% CI 0.16-0.40) and non-vertebral fractures (HR 0.75, 95% CI 0.57-0.97) was lower in the romosozumab/denosumab group than in the placebo/denosumab group. In the second year, there were 5 new vertebral fractures in the romosozumab/denosumab group and 25 in the placebo/denosumab group. During the second 12-month period there was one additional case of osteonecrosis of the jaw in the group treated with romosozumab followed by denosumab.

The HORIZON Study – Zoledronic Acid[51]

The HORIZON study randomized 7,765 patients to annual IV infusions of zoledronic acid 5 mg or identical placebo and followed them for 36 months.[51] The participants were women ages 65 to 90 years with BMD T-scores less than –2.5 or prior vertebral fracture with T-score less than -1.5. Mean

total hip T-score was not reported, but 63% had vertebral fractures at baseline. The co-primary outcomes were the cumulative incidence of new vertebral fractures and hip fractures. New vertebral fractures occurred in 3.3% of women in the zoledronic acid group and 10.9% of women in the placebo group (RR 0.30, 95% CI 0.24-0.38). Non-vertebral fractures occurred in 8.0% of women in the zoledronic acid group and 10.7% of women in the placebo group (RR 0.75, 95% CI 0.64-0.87). Hip fractures occurred in 1.4% of women in the zoledronic acid group and 2.5% of women in the placebo group (RR 0.59, 95% CI 0.42-0.83). The treatment effects were consistent over time with similar reductions in vertebral fractures at years one, two, and three (RR 0.40, 0.29, and 0.30 respectively, $p<0.001$ at all 3 time points). There was no evidence of a delay in efficacy for vertebral fractures, non-vertebral fractures, hip fractures, or any clinical fractures.

Discontinuation of the study drug due to adverse events was similar in the two groups (2.1% vs. 1.8%). During the three days following the infusion, more patients in the zoledronic acid group reported fever (16.1% vs. 2.1%), myalgias (9.5% vs. 1.7%), and flu-like symptoms (7.8% vs. 1.6%). The post-infusion symptoms decreased over time (first infusion 31.6%; second 6.6%, third 2.8%). Adherence was greater than 90% in both groups.

Quality of Individual Studies

Using the USPSTF criteria, we rated the three studies to be of good quality (Appendix Table E4). The trials all used appropriate randomization methods with comparable groups at baseline and good retention to retain comparability through the end of the study periods. The studies were all double-blinded with clearly defined interventions and blinded adjudication of outcomes. The key outcomes were addressed and appropriate intention-to-treat analyses were performed. The only exception is for the teriparatide group in the ACTIVE study. The abaloparatide and placebo groups were double-blind, but the teriparatide group received open label treatment. For this reason, we performed sensitivity analyses with and without data from this arm of the ACTIVE study in our NMAs. The HORIZON study was also rated as good quality.

Clinical Benefits

The essential clinical benefit of the anabolic drugs for osteoporosis is the prevention of fragility fractures. The primary outcome in the pivotal trials was incident morphometric vertebral fractures, even though more than half of these fractures are not clinically apparent. Non-vertebral fragility fractures were also reported as they are relatively common and clinically important. Finally, hip fractures are clinically the most important in terms of impact on a patient's quality of life, but they are uncommon. All three anabolic studies had insufficient power to demonstrate a reduction in hip fractures. However, the HORIZON study demonstrated that zoledronic acid significantly reduced the incidence of hip fractures in women with osteoporosis.[51]

Vertebral Fractures

The pivotal trials of teriparatide, abaloparatide, and romosozumab all reported a significant reduction in vertebral fractures (Appendix Table E6). The results of the NMA confirmed this finding (Table 4). All four drugs were significantly better than placebo. None of the three anabolic agents were significantly different from each other, nor were they significantly different from zoledronic acid. There was a trend towards abaloparatide being more effective than the other three drugs, but the credible intervals for all three drugs contained 1. The ACTIVE trial did not report the HR for abaloparatide versus teriparatide for vertebral fractures.

Table 4. Network Meta-Analysis Results for the Relative Risk of Vertebral Fractures*

Abaloparatide (80 mcg)				
0.51 (0.13 – 1.52)	**Romosozumab (210 mg)**			
0.50 (0.14 – 1.34)	0.98 (0.48 – 1.92)	**Teriparatide (20 mcg)**		
0.49 (0.14 – 1.28)	0.96 (0.52 – 1.67)	0.98 (0.60 – 1.57)	**Zoledronic Acid (5 mg)**	
0.14 (0.04 – 0.36)	**0.27 (0.16 – 0.47)**	**0.28 (0.18 – 0.43)**	**0.29 (0.23 – 0.37)**	**Placebo**

*Includes data from open-label teriparatide arm of the ACTIVE trial

Legend: The drugs are arranged from most effective (top left) to least effective (bottom right) based upon placebo comparisons. Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1

Non-Vertebral Fragility Fractures

In the key randomized trials, both teriparatide and abaloparatide significantly reduced non-vertebral fractures (Appendix Table E6). The results of the NMA confirmed this finding (Table 5). Again, none of the three anabolic agents were significantly different from one another, nor were they significantly different from zoledronic acid. Note that zoledronic acid significantly reduced non-vertebral fractures in the pivotal HORIZON trial and in the NMA. In the ACTIVE trial, the HR for abaloparatide compared to teriparatide was 0.79 (95% CI 0.43-1.45), which is nearly identical to the estimate from our NMA.

Table 5. Network Meta-Analysis Results for the Relative Risk of Non-Vertebral Fragility Fractures*

Abaloparatide (80 mcg)				
0.81 (0.45 – 1.44)	**Teriparatide (20 mcg)**			
0.69 (0.38 – 1.17)	0.83 (0.54 – 1.26)	**Zoledronic Acid (5 mg)**		
0.66 (0.33 – 1.28)	0.81 (0.46 – 1.42)	0.99 (0.65 – 1.50)	**Romosozumab (210 mg)**	
0.54 (0.30 – 0.92)	**0.65 (0.44 – 0.98)**	**0.79 (0.67 – 0.93)**	0.80 (0.55 – 1.14)	**Placebo**

*Includes data from open-label teriparatide arm of the ACTIVE trial

Legend: The drugs are arranged from most effective (top left) to least effective (bottom right) based upon placebo comparisons. Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1

Hip Fractures

Among the anabolic studies the incidence of hip fractures was low, so only the FRAME study reported relative risks (Appendix Table E6), while hip fractures were reduced in the HORIZON trial (RH=0.59, CI 0.42-0.83). The relatively large one year FRAME study was underpowered to detect a significant reduction in hip fractures with romosozumab, even though the observed reduction was almost 50%. The results of the NMA improve the precision of the estimates, so that both romosozumab and teriparatide significantly reduce hip fractures compared to placebo (Appendix Table E8). The relative risk estimates for abaloparatide and teriparatide were based on just a handful of fractures and were unrealistically low (much lower than the estimates for vertebral fractures, which has not been observed for any other drug used to prevent fractures). Given the instability of these estimates, we do not think that they should be used in assessing the comparative effectiveness of these drugs. Again, none of the three anabolic agents were significantly different from each other, nor were they significantly different from zoledronic acid. Note that zoledronic acid significantly reduced hip fractures in both the pivotal HORIZON trial and the NMA.

Bone Mineral Density

Change in BMD is often used as a surrogate marker in preliminary studies of drugs to prevent osteoporotic fractures. The change in BMD for the anabolic agents and zoledronic acid in the pivotal trials are summarized in Appendix Table E7. The anabolic agents had large increases in BMD of the lumbar spine (approximately 10% to 13% over 12 to 21 months), while zoledronic acid had

smaller gains (6.7% over 36 months). At the total hip, the increases compared to placebo were greatest for romosozumab (6.9%) and zoledronic acid (6.0%), with somewhat smaller gains for abaloparatide (4.3%) and teriparatide (3.6%). The changes in BMD at the femoral neck were similar to those observed at the total hip. Because change in BMD is an imperfect predictor of fracture prevention, it is difficult to draw firm conclusions from these results.

Harms

Table 6 summarizes the harms of the anabolic therapies observed in the clinical trials. There were no important differences in serious adverse events between the anabolic therapy groups and placebo groups. In the ACTIVE trial, the abaloparatide group had a greater percentage of patients discontinue therapy due to adverse events than the teriparatide or placebo groups, but the difference was small (10% vs. 7% and 6%, respectively). There was one case of osteonecrosis of the jaw and one atypical femoral fracture observed during the one year of treatment with romosozumab during the FRAME trial, but these may be chance findings. Similarly, there was one case of osteonecrosis of the jaw observed in the placebo group of the HORIZON trial. No other cases of osteosarcoma were observed in any of the trials. As described in the Key Trials section above, there were more cases of hypercalcemia with teriparatide and abaloparatide and more injection site reactions with romosozumab, but most were mild and self-limited, though some required dose reduction or a decrease in calcium supplementation.

Table 6. Key Harms in Randomized Trials of Anabolic Agents for Osteoporosis

Reference	Group	SAEs	Discontinuation due to AE	AFF	ONJ	Kidney stones	Hyper-Ca
Teriparatide							
Neer 2001[49]	Teriparatide Placebo	NR NR	6% 6%	NR NR	NR NR	No sign. diff.	11% 2%
Abaloparatide							
Miller 2016[5]	Abaloparatide Teriparatide Placebo	9.7% 10.0% 11.0%	9.9% 6.8% 6.1%	NR NR	NR NR	NR NR	3.4% 6.4% 0.4%
Romosozumab							
Cosman 2016[48]	Romosozumab Placebo	9.6% 8.7%	2.9% 2.6%	1 0	1 0	NR NR	NR NR
Key comparator: Zoledronic acid							
Black 2007[51]	Zoledronic acid Placebo	29.2% 30.1%	2.1% 1.8%	NR NR	1 1	NR NR	NR NR

AE: adverse event, AFF: atypical femoral fracture, Hyper-ca: hypercalcemia, NR: not reported
ONJ: osteonecrosis of the jaw, SAE: serious adverse event

Additional considerations include the perceived risk for atypical femoral fractures and osteonecrosis of the jaw with bisphosphonates. In addition, a substantial proportion of patients report systemic symptoms following zoledronic acid infusion, which may contribute to decreased long-term adherence. This may be an issue for the injectable anabolic agents as well, as one study found the discontinuation rates of teriparatide after one year were higher than those of zoledronic acid.[10]

Sensitivity Analyses

There were insufficient studies to perform meta-regression and we did not have individual level data that would have allowed for subgroup analyses. We did repeat the NMA eliminating the teriparatide data derived from the open-label arm of the ACTIVE trial. There were no changes in the conclusions from the NMAs and the changes in the estimates for teriparatide were modest (a slight reduction in efficacy for vertebral and hip fractures, and a slight increase in the reduction of non-vertebral fractures (Appendix Tables E9-10).

Controversies and Uncertainties

The primary controversy to address is whether it was appropriate to combine the data from the different study populations of the four trials in a NMA. There were clear differences in the inclusion criteria of the studies (Appendix Table E2) and in some of the characteristics of patients included in the study, though all were women and the average age and BMI of the participants was very similar across the trials (Appendix Table E3). In order for the differences to be problematic, there must be differences in the relative risks for fracture for one or more of the drugs in one subgroup compared to another. Specific analyses looking for effect modification by patient characteristics such as age, BMD, prior fracture history, and baseline risk for fracture have been published for teriparatide[52], abaloparatide[53], and romosozumab.[48] In all three analyses, risk factors for fracture did not modify the efficacy of the drugs. In the FRAME trial, romosozumab appeared to be less effective in participants recruited in Latin America, but this observation was of borderline statistical significance. Given the number of subgroups examined, this may be a chance finding. This finding deserves additional attention, but is not strong enough to invalidate the NMA.

It is also worth examining the incidence of fractures in the placebo groups in each of the four pivotal trials as an indicator of the underlying risk for fractures in patients enrolled in the trials (Table 7).

Table 7. Annual Incidence of Vertebral, Non-Vertebral, and Hip Fractures in Placebo Groups

Reference	Trial	Vertebral Fx	Non-Vertebral Fx*	Hip Fx
Teriparatide	Fracture Prevention Trial	6.7	3.1	0.4
Abaloparatide	ACTIVE	2.4	2.7	0.2
Romosozumab	FRAME	1.8	2.1	0.4
Zoledronic acid	HORIZON	3.6	3.6	0.8

Fx: fracture

*Includes hip fractures

The annual risk for vertebral fractures was particularly high in the Fracture Prevention Trial because all participants had prior vertebral fractures. The annual vertebral fracture rates in the other trials were higher in the trials with greater prevalence of vertebral fractures at baseline (Appendix Table E1). For non-vertebral fragility fractures and hip fractures, the annual risks were reasonably similar across the trials. It is worth noting that patients in the HORIZON trial were at as high or higher risk for fracture as patients included in the pivotal trials of the anabolic agents.

A major area of uncertainty was the relative paucity of evidence for each of the anabolic agents, particularly for the hip fracture outcome. The trials were relatively small given the large number of women with osteoporosis. In addition, the active treatment continued for only one to two years. We could not model stable estimates for hip fracture reduction because of the low number of events.

Some have suggested that anabolic therapy may have more rapid onset of fracture prevention than antiresorptive therapy. Given the paucity of head-to-head trials, it is difficult to evaluate this hypothesis. In the HORIZON trial, the reductions in hip fractures, non-vertebral fractures, and any clinical fractures, as assessed by the Kaplan-Meier curves, appeared to begin at randomization. The reduction in clinical vertebral fractures may have been delayed, but is unlikely to be clinically or statistically significant. In the ACTIVE trial, abaloparatide appeared to have a more rapid reduction in non-vertebral fractures, clinical fractures, and major osteoporotic fractures than teriparatide, but the differences were not statistically significant except for major osteoporotic fractures (p=0.03). The Kaplan-Meier curves for clinical vertebral fractures were not shown. There are insufficient data to assess the relative efficacy of the anabolic agents compared to zoledronic acid in the first three to six months of therapy. There are no significant differences in fracture reduction between anabolic therapy and zoledronic acid over longer time periods.

Another important area of uncertainty is sequencing of therapies. Studies suggest that the bone density gains from anabolic agents are quickly lost if no follow-up therapy is used.[54] Since anabolic agents are only used for one to two years, they will need to be followed by some form of anti-resorptive therapy to maintain the reduction in fracture risk. Other studies have found that the beneficial effects of PTH-related therapies on bone mass are blunted among individuals switched

from anti-resorptive therapies.[55] The best agent to use and the optimal length of follow-up treatment is uncertain and awaits additional fracture endpoint studies.

The outcomes of greatest interest to patients are maintenance of independence and prevention of disability. These and other patient-centered outcomes were not reported in the pivotal trials.

Summary

The evidence to date demonstrates with high certainty that the anabolic agents reduce vertebral fractures compared to no therapy, with abaloparatide demonstrating the greatest reduction in vertebral fractures. However, there is insufficient evidence to distinguish the anabolic agents from each other and from zoledronic acid for vertebral fractures. The differences in fracture reduction are small and the credible intervals all contain 1, so the therapies may be comparable. The evidence is even less certain for non-vertebral fragility fractures and, in particular, hip fractures. The harms of therapy are relatively small and have little influence on the net benefit for each therapy compared to the others. Adherence to therapy is essential, both initial anabolic therapy and subsequent anti-resorptive therapy to preserve the fracture reduction benefit. However, there are minimal real-world data available to compare adherence to therapy among the three anabolic agents.

For each of the three anabolic agents, we judge the evidence to be promising, but inconclusive (P/I) for the net health benefit when compared to zoledronic acid in postmenopausal women with osteoporosis at high risk for fracture.

When compared to no treatment, we judged with moderate certainty that the anabolic agents provided a small or substantial net health benefit compared to no therapy, with high certainty of at least a small net health benefit when compared to no therapy (B+). There is a substantial reduction in vertebral fractures, a small to moderate reduction in nonvertebral fractures, and uncertain benefits for hip fractures.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness.

1. Unmeasured patient health benefits: There are no clear differences among the drugs.

2. Relative complexity of the treatment regimen that is likely or demonstrated to significantly affect adherence and outcomes: There are important differences in the treatments that may be important for some patients and preferences will differ among patients. Abaloparatide and teriparatide require daily injections, which is a barrier to adherence for some patients. Romosozumab is a monthly injection that may require an office visit to monitor for hypersensitivity reactions. This may be a deterrent for some patients, but may enhance adherence for others. Finally, the comparator, zoledronic acid requires an annual visit for a 15-minute infusion that can be associated with systemic symptoms, particularly following the first dose. The once-a-year dosing may be an advantage, but the requirement for an intravenous infusion may decrease acceptability. In addition, some patients may have concerns about a drug that remains in the body for a long time.

3. Impact on productivity and ability of the patient to contribute to personal and national economic activity: No clear differences among the different drugs.

4. Impact on caregiver burden: No clear differences among the drugs, although daily injections may be burdensome if a caregiver is required to perform the injection.

5. Impact on spread of infectious disease: Not applicable.

6. New mechanism of action that is likely to help patients who have not responded to other treatments: Abaloparatide acts through the same mechanism as teriparatide. Romosozumab has a unique mechanism of action. However, to date, there is no subgroup known to respond more to a drug from one specific class.

7. Severity of the untreated condition: Based upon fracture outcomes in controlled trials, no clear differences among the different drugs

8. Lifetime burden of illness: No clear differences among the different drugs

9. Lack of availability of any previous treatment for the condition: There are existing anabolic and anti-resorptive treatments for osteoporosis.

10. Other ethical, legal, or social considerations that might strongly influence the overall value of an intervention to patients, families, and caregivers, the health system, or society: There are no clear differences among the drugs.

6. Long-Term Cost Effectiveness

6.1 Overview

We conducted a cost-effectiveness analysis using a simulation model comparing anabolic therapies versus treatment with a bisphosphonate (zoledronic acid) in a representative cohort of postmenopausal women who are at high risk for osteoporotic fractures. Zoledronic acid was chosen as a comparator because 1) it is commonly used, 2) adherence with treatment is significantly higher than with oral bisphosphonates, and 3) patients at higher risk of fracture are likely to receive this drug. We estimated the incremental costs, quality-adjusted survival, and cost-effectiveness of osteoporosis drugs relative to zoledronic acid, using estimates of relevant clinical parameters from trial data and estimates of drug and other related health care costs.

Model outcomes of interest include:

- Incidence of clinical vertebral and nonvertebral (distinguished as hip and other) fractures
- Life expectancy
- Quality-adjusted life-years (QALYs)
- Osteoporosis drug treatment costs
- Fracture costs
- Total costs
- Costs per QALY gained

6.2 Cost-Effectiveness Model: Methods

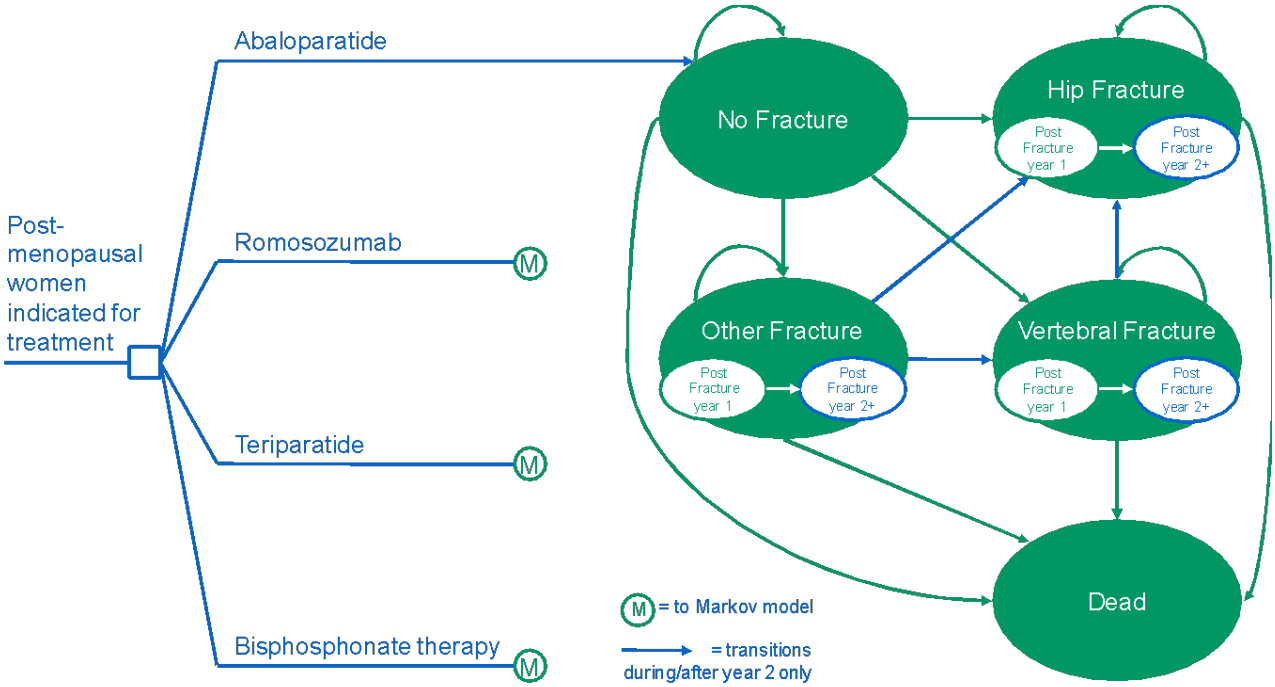
Model Structure

The primary aim of this analysis was to estimate the cost-effectiveness from a health system perspective of various treatments indicated for the prevention of osteoporotic fractures in postmenopausal women who have not been recently treated for osteoporosis but who have an indication for treatment to prevent osteoporotic fractures. The model structure is depicted in Figure 3, and is based in part on a literature review of prior published models of osteoporosis.[56] A representative cohort of patients at high fracture risk who are untreated or have not recently received treatment transitions between health states during one-year cycles over a lifetime time horizon, modeling patients from treatment initiation until death.

The model consists of several health states, including osteoporosis without a new fracture (the origination state for patients entering the model), vertebral fracture (clinical or morphometric), hip fracture, other fracture (including wrist or tibia fracture), and death. Patients enter an acute

fracture health state for one year upon experiencing a new fracture; after one year, patients transition to a post-fracture health state, where they remain until they transition to a subsequent fracture or death. Once they enter a post-fracture health state, patients may only transition to a worse subsequent fracture or die, so that patients who experience a serious fracture do not forfeit the long-term costs and utilities associated with it by transitioning to a less severe fracture in the "memory-less" Markov model framework. The assumed hierarchy of fracture severity is hip > vertebral > other. All hypothetical patients are modeled until death.

Figure 3. Markov Model Structure for Osteoporosis Patients



Target Population

The population of focus is postmenopausal women who have not been recently treated for osteoporosis, but who have an indication for treatment to prevent osteoporotic fractures. In our base-case analysis, we assumed the fracture risk was similar to that observed in the clinical trials of the anabolic agents; this estimate was varied in a scenario analysis. Patients were assumed to enter the cohort at age 70 years, based on the demographic data from the pivotal trials of the anabolic agents, in which average age was 68.8 – 70.9 years.[5,48,49]

Key Model Characteristics

The model utilizes results from the network meta-analysis (NMA) of multiple trials to derive effectiveness estimates for fracture prevention for each drug regimen (see Table 9). We applied the relative risk estimates derived from the NMA to the baseline fracture probabilities, which were

derived from a combination of clinical trials, the published literature, and the FRAX Fracture Risk Assessment Tool.[5,48,49,57-59] Survival time in each health state was weighted by published health state-specific utilities to model health-related quality of life. The model includes separate utilities for the different types of fractures.[60] Patient mortality was based on US background age-related mortality estimates for females; hip fractures could increase the risk of mortality.

The model includes treatment costs associated with each individual regimen, including drug acquisition costs and acute care costs for fractures. The base-case analysis uses a health care system perspective (i.e., focuses on direct medical care costs only). All costs and health outcomes were discounted by 3% per year.[61]

Key Model Assumptions

Table 8 contains a list of key model assumptions along with the rationale for each assumption.

Table 8. Key Model Assumptions

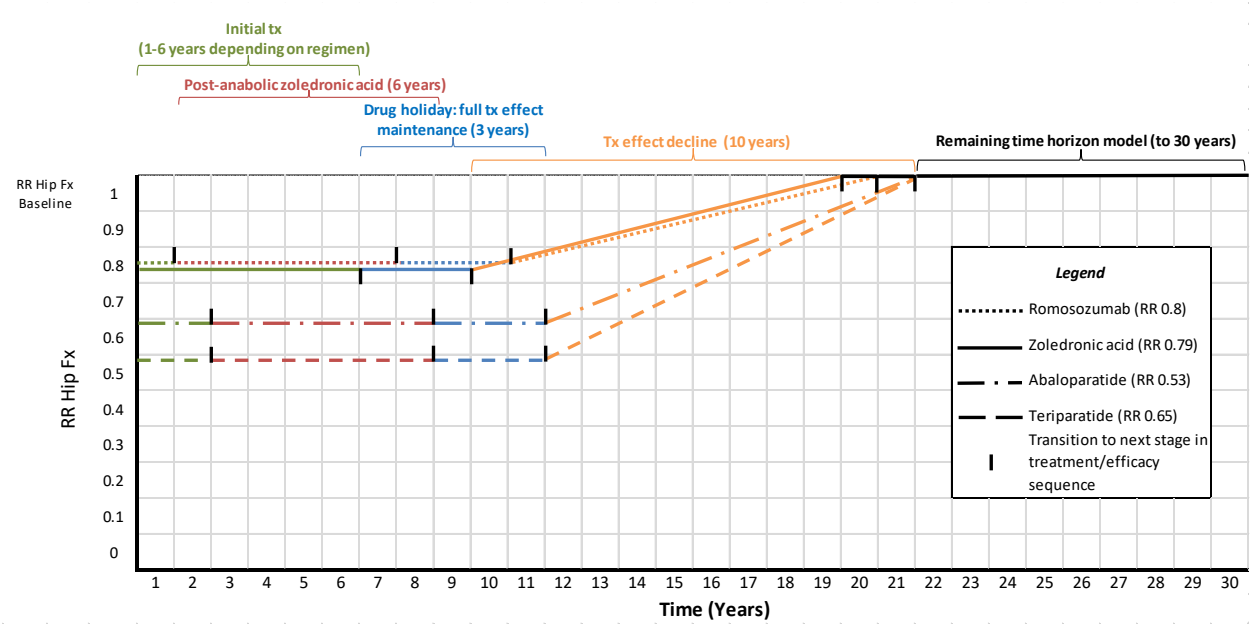
Assumption	Rationale
Patients may have an unlimited number of fractures over the modeled time horizon.	Real-world patients may experience any number of fractures.
From a post-fracture state, patients can transition to a worse fracture state only (or death). The hierarchy for fracture severity is hip > vertebral > other.	Prevents patients who experience more serious fractures from forfeiting serious fracture states' associated long-term costs and utilities by transitioning to a less severe fracture in the "memory-less" Markov model framework.
Hip fracture relative risk estimates reflect all non-vertebral fractures in the base case analysis, effectively combining hip and other fractures. In a scenario analysis, we consider hip fracture relative risk estimates derived separately from other fractures.	Trial-observed hip fractures were rare, and NMA results for hip-only fractures lacked face validity due to the small number of events in the pivotal trials of anabolic agents.
We did not model serious adverse events.	Anabolic regimens as well as zoledronic acid exhibited similar serious adverse event rates compared to placebo and each other in their respective trials. These small event rate differences are unlikely to impact cost-effectiveness results.
All anabolic therapies are administered for a duration of one to two years according to trial data (abaloparatide: two years, romosozumab: two years) or drug label (teriparatide: two years), followed by six years of zoledronic acid. We assume that time to benefit for anabolic agents and zoledronic acid is similar and that 100% anabolic efficacy is maintained throughout the anabolic and bisphosphonate periods plus an additional 3 years, then efficacy declines linearly to a relative risk of 1 over a period of 10 years.	Anabolic treatment duration: Best available evidence Zoledronic acid treatment duration: AACE guidelines state that patients at high risk should be treated for six years. The HORIZON Extension Trial demonstrated added efficacy for six but not nine years of therapy and maintenance of efficacy for three years following treatment cessation. Time to benefit: Data show that the benefit of treatment is immediate for hip fracture and for any clinical fracture. Efficacy maintenance: Expert opinion. Efficacy decline: Parity with previous cost-effectiveness models that model a decline over time.
Bisphosphonate therapy with zoledronic acid is administered for six years, 100% efficacy is maintained throughout the six-year administration period plus an additional three years, then efficacy declines linearly to a relative risk of 1 over a period of 10 years.	See above.
All comparators' adherence rates were 100% in base case analysis.	Lack of real-world adherence data for newer anabolic agents (abaloparatide & romosozumab), and on the impact of lower adherence on efficacy for all three anabolics.
Parity pricing for romosozumab is modeled based on the cost per pen of teriparatide.	Drug awaiting approval, no pricing data are available. Parity with teriparatide price/pen was suggested by manufacturer. Pricing is further explored in threshold analyses.
We applied a 27% discount to the WAC price of abaloparatide.	Net price information for abaloparatide is not yet available. The average industry-wide reduction (including discounts, rebates and other price concessions) for brand drugs is 27.1%.[62]

Treatment Strategies

The interventions assessed in the model were the same as those in the clinical evidence review (abaloparatide, teriparatide, romosozumab, and zoledronic acid). We compared all the anabolic agents to zoledronic acid in the base-case analysis, which allowed us to evaluate the relative incremental benefits and harms of these agents when used first-line in patients with risk for fragility fractures.

All patients received treatment upon entering the model. Anabolic therapy patients were treated for one to two years depending on drug (abaloparatide: two years, romosozumab: one year, teriparatide: two years), immediately followed by six years of therapy with zoledronic acid. We assumed anabolic therapies had 100% efficacy throughout the treatment regimen (i.e., no efficacy ramp-up time), that time to benefit was similar between anabolic agents and zoledronic acid, and that anabolic therapies' efficacy was then maintained throughout the zoledronic acid administration period plus three years before declining to a relative risk of 1 over a 10-year period. For zoledronic acid, we modeled a three-year efficacy maintenance period after the administration period ended, followed by an efficacy decline over 10 years. We assumed complete regimen adherence for all agents. Figure 4 represents an example of treatment sequencing and effect over time for hip fractures; the same approach applied to vertebral and to other fractures. We explored the impacts of our assumptions regarding efficacy onset, maintenance, and decline in scenario analyses.

Figure 4. Treatment Sequencing and Effect Over Time for Hip Fractures



Note: Each treatment line is color-coded to match the X-axis labels at the top of the chart; vertical black lines indicate transitions to the next stage in sequence/efficacy. Line placement is not exact.
Fx: fracture, RR: relative risk, Tx: treatment

Clinical Inputs

Annual relative fracture risk estimates for each drug were derived from the ICER NMA (Table 9); each relative risk estimate represents the differential risk of fracture versus placebo per year. In probabilistic sensitivity analyses (PSA), relative risk estimates were varied using a log-normal distribution.

Table 9. Fracture Relative Risk Parameters

Model Input	Default	Lower	Upper	Source
Zoledronic acid (baseline)				
Vertebral Fracture	0.29	0.23	0.37	NMA
Non-Vertebral Fractures*	0.79	0.67	0.93	NMA
Abaloparatide				
Vertebral Fracture	0.14	0.04	0.36	NMA
Non-Vertebral Fractures*	0.53	0.30	0.91	NMA
Romosozumab				
Vertebral Fracture	0.27	0.16	0.47	NMA
Non-Vertebral Fractures*	0.80	0.54	1.14	NMA
Teriparatide				
Vertebral Fracture	0.28	0.18	0.43	NMA
Non-Vertebral Fractures*	0.65	0.43	0.98	NMA

*Relative risks for non-vertebral fractures were used for all non-vertebral fractures in the base-case analysis, including hip fractures

Baseline Fracture Inputs

The relative risk estimates from the NMA were applied to age-stratified baseline (placebo) estimates of annual fracture risk to derive each comparator's annual fracture probabilities (Table 10). We derived the baseline annual fracture probabilities for the average 70-year old patient from the pooled placebo arms of the Fracture Prevention, ACTIVE, FRAME, and HORIZON trials.

To model increasing fracture risk as patients age, we extrapolated these estimates for a 70 year old based on previously published age-stratified fracture estimates[57] and 10-year probability of fracture based on FRAX Fracture Risk Assessment Tool output for a 70-year-old US Caucasian woman with a T-score of -3.[60] First, we used Melton et al. for age-weighted estimates of the increasing risk of fracture over time. These estimates are for a mixed population of people with and without a prior fracture, so are higher than for someone who has never had a fracture but somewhat lower than for someone who has. We then calibrated hip fracture estimates so the modeled 10-year cumulative incidence of hip fracture matched the FRAX 10-year probability of hip fracture (9.3%). Each resultant estimate was varied by ±20% in sensitivity analyses. Annual probabilities were linearly interpolated from the five-year estimates. All baseline fracture parameters were varied using a beta distribution in the PSA.

Table 10. Baseline (Placebo) Annual Fracture Probabilities by Age Strata

Fracture and Age Groups	Default	Lower	Upper	Source
Hip Fracture				
Age 70-74	0.006	0.005	0.007	Pooled trials
Age 75-79	0.011	0.009	0.013	Pooled trials & Melton[57]/FRAX extrapolation
Age 80-84	0.023	0.019	0.028	Pooled trials & Melton/FRAX extrapolation
Age 85+	0.031	0.025	0.038	Pooled trials & Melton/FRAX extrapolation
Vertebral Fracture				
Age 70-74	0.034	0.027	0.041	Pooled trials
Age 75-79	0.046	0.037	0.055	Pooled trials & Melton extrapolation
Age 80-84	0.076	0.061	0.091	Pooled trials & Melton extrapolation
Age 85+	0.091	0.074	0.111	Pooled trials & Melton extrapolation
Other Fracture				
Age 70-74	0.024	0.019	0.029	Pooled trials
Age 75-79	0.037	0.030	0.044	Pooled trials & Melton extrapolation
Age 80-84	0.053	0.042	0.063	Pooled trials & Melton extrapolation
Age 85+	0.079	0.063	0.095	Pooled trials & Melton extrapolation

Fracture-Related Excess Mortality Inputs

A review of studies reporting excess mortality following fractures showed that most studies did not control for comorbidities. The one study that did control for underlying health status found that excess mortality only occurred after hip fractures (i.e., not after other fragility fractures), and at a rate roughly 50% lower than studies that adjusted for age and gender only.[63] We therefore applied fracture-related excess mortality to hip fractures only, by applying the Tosteson formula (=[baseline probability *{hazard ratio-1}]/[baseline probability*{hazard ratio-1}+1]) to baseline hip fracture probabilities (Table 11). The excess mortality estimates were then added to US background mortality estimates at each model cycle for hip fracture patients.[60] All excess mortality parameters were varied using a log-normal distribution in a PSA.

Table 11. Absolute Mortality Increase for Hip Fracture

Age Range	Default	Lower	Upper	Source
Age 70-74	0.0025	0.0020	0.0029	Tosteson[63]
Age 75-79	0.0075	0.0060	0.0090	Tosteson
Age 80-84	0.0336	0.0269	0.0403	Tosteson
Age 85+	0.0727	0.0581	0.0872	Tosteson

Quality-of-Life Inputs

Health state utilities were derived from publicly-available literature and/or manufacturer-submitted data, and applied to the fracture and post-fracture health states (Table 12).[64-68] We used baseline

utility estimates for patients with no new fracture, and applied utility multipliers for each fracture health state. The utility multipliers for vertebral fracture were applied to only 35% of patients with vertebral fracture, reflecting the proportion of these fractures that were clinical fractures in a retrospective cohort analysis;[57] non-clinical vertebral fractures had no utility multiplier applied. Health state utility values did not vary across treatments evaluated in the model. All utility parameters were varied using a beta distribution in the PSA.

Table 12. Utility Values by Age Strata and Utility Multipliers

Model Input	Default	Lower	Upper	Source
General Population Utilities				
Age 50-59	0.840	0.672	1.000	Hanmer et al.[64]
Age 60-69	0.810	0.648	0.972	Hanmer et al.
Age 70-79	0.770	0.616	0.924	Hanmer et al.
Age 80+	0.720	0.576	0.864	Hanmer et al.
Utility Multipliers				
Hip Fracture Year 1	0.700	0.560	0.840	Peasgood et al.[67]
Hip Fracture Year 2+	0.800	0.640	0.960	Peasgood et al.
Vertebral Fracture Year 1	0.590	0.472	0.708	Peasgood et al.
Vertebral Fracture Year 2+	0.931	0.745	1.000	Kanis/Oleksik et al.[65,66]
Other Fracture Year 1	0.902	0.722	1.000	Burstrom et al.[68]
Other Fracture Year 2+	1.000	0.800	1.000	Assumption

Drug Cost Inputs

We used the average wholesale acquisition cost (WAC) for generic zoledronic acid and assumed that treatment was administered for six years.[69] For the price of teriparatide, we obtained data from SSR Health that combined information on net US dollar sales through the third quarter of 2016 with information on unit sales to derive net pricing at the unit level across all payer types.[70] We estimated net prices by comparing the four-quarter rolling averages (i.e., last quarter of 2015 through third quarter of 2016) of both net prices and WAC per unit to arrive at a mean discount from WAC for the drug. Finally, we applied this average discount to the WAC as of April 2017[69] to arrive at an estimated net price. The derived discount for teriparatide was 40%, which was then applied to the WAC for a 2.4 ml (250 mcg/ml) package that resulted in a net price of $1,628.45. This discount may not reflect the negotiated price for any one payer, but rather the average discount across all payers. For abaloparatide, we used the announced list price of $1,625 per pen and applied a 27% discount, representing the average industry-wide discount on brand drugs.[62,71] Because romosozumab has yet to receive FDA approval and does not have a price, we used the teriparatide cost per pen as a benchmark. In addition, threshold analyses on these costs are provided in Section 6.3. All drug costs were varied by ±20% using a normal distribution in the PSA.

Table 13. Drug Cost Inputs

Drug Name, Labeled Dose, Administration Route	Strength (Package Size)	WAC/Package	Net Price*	Base-case Tx Duration	Acquisition Cost Per Tx Course†
Teriparatide 20 mcg SC QD	250 mcg/ml (2.4 mL)	$2,727.84	$1,628.45‡	2 years	$42,485
Abaloparatide 80 mcg SC QD	3,120 mcg/1.56 mL	$1,625	$1,186.25§	2 years	$29,312
Romosozumab 210 mcg SC Q mo	N/A	N/A	$1,628.45#	1 year	$19,541
Zoledronic Acid 5 mg IV Q year	4 mg/5 mL	197¤	197¤	6 years	$1,182

IV: intravenous, SC: subcutaneous, QD: once daily, Q mo: once montly, Q year: once yearly, Tx: treatment, WAC: wholesale acquisition cost

*Net price is the estimated price after discounts and rebates from WAC. No discounts have been applied to generic zoledronic acid.

†Acquisition cost of initial drug using net price (or average generic WAC for zoledronic acid) and assuming full course of treatment; costs would be lower if a modeled patient died before completing a course of therapy. Costs do not include the additional costs of post-anabolic zoledronic acid therapy.

‡Price per pen including 40% discount

§Price per pen based on announced list price and assumed 27% discount

#Monthly price based on parity pricing with teriparatide discounted price per pen

¤Annual dose cost based on average generic WAC

Healthcare Cost Inputs

Fracture-related healthcare costs were derived from publicly available literature, and applied to the fracture and post-fracture health states (Table 14).[72,73] All cost estimates were from US cohort studies in representative populations, and inflated to 2016 US dollars. Costs for vertebral fracture were applied to only 35% of patients, reflecting the proportion of clinical vertebral fractures in a retrospective cohort;[57] non-clinical vertebral fractures had no fracture-related costs applied. We did not model administration costs as anabolic drugs are self-administered, and we assumed supportive care costs were similar among comparators and thus would not contribute to cost differences. All healthcare costs were varied by ±20% using a log-normal distribution in the PSA.

Table 14. Acute and Long-Term Annual Fracture Costs

Model Input	Default	Lower	Upper	Source
Hip Fracture Cost	$23,253	$18,602	$27,903	Shi[73]
Post-Hip Fracture Annual Cost	$10,835	$8,668	$13,002	Parthan[72]
Vertebral Fracture Cost	$11,450	$9,160	$13,740	Shi
Post-Vertebral Fracture Annual Cost	$309	$247	$371	Parthan
Other Fracture Cost	$9,869	$7,895	$11,843	Shi
Post-Other Fracture Annual Cost	$0	$0	$0	Parthan

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes. One-way sensitivity analyses used 95% confidence intervals from clinical evidence where available. When 95% confidence intervals were not available, uncertainty ranges were varied by ±20%. We also conducted a PSA by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome (Appendix Tables F1-F2).

In addition, we also conducted scenario analyses to explore the impacts of our assumptions on model results, by varying:

1. Baseline fracture risk probabilities, by increasing the baseline fracture rates by up to 100%.
2. Years of maintenance of full treatment effect after stopping zoledronic acid treatment.
3. The duration of the efficacy decline for anabolic agents, including no decline over lifetime horizon.
4. Zoledronic acid ramp-up time to full efficacy (base case was full efficacy throughout).
5. Comparison to no treatment, rather than to zoledronic acid.
6. NMA relative risk estimates by excluding open-label teriparatide data from the ACTIVE trial.
7. Increased relative risk of subsequent fracture.
8. Hip fracture relative risks using an NMA that derived hip fracture estimates separately from other fractures; hip fracture was a rare event in the clinical trials, therefore these estimates are highly uncertain and were not used in the base-case analysis.
9. *(Planned for release in the subsequent version of the report)* Duration of teriparatide and abaloparatide therapy as studied in the trials (i.e., 21 and 18 months, respectively, vs. the labeled indication of two years in the base case)

6.3 Cost-Effectiveness Model: Results

Base Case Results

Each anabolic therapy resulted in increased costs, QALYs, and life years compared to zoledronic acid (Table 15). QALYs gained versus zoledronic acid ranged from 0.004 for romosozumab to 0.071 for abaloparatide over the lifetime horizon (Table 16). Incremental costs ranged from a low of $19,249 for romosozumab to $38,448 for teriparatide. The base case incremental cost-effectiveness ratios (ICERs) for each anabolic drug compared to zoledronic acid far exceeded the commonly-cited cost-effectiveness threshold of $150,000 per QALY (Table 16).

Table 15. Base-Case Results

Regimen	Cost	QALYs	Life Years
Zoledronic acid	$17,851	8.953	12.202
Romosozumab	$37,100	8.957	12.202
Teriparatide	$56,298	8.989	12.205
Abaloparatide*	$40,522	9.028	12.208

QALY: quality-adjusted life year

Table 16. Pairwise Results for Anabolic Therapies Compared to Zoledronic Acid

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Abaloparatide	$22,671	0.075	0.006	$303,584
Teriparatide	$38,448	0.037	0.004	$1,052,824
Romosozumab	$19,249	0.004	<0.001	$4,388,095

ICER: incremental cost-effectiveness ratio, Incr.: incremental, LY: life year, QALY: quality-adjusted life year

Appendix Tables F1-F2 provide additional detail regarding the model findings. First, there were small to moderate cost offsets compared to zoledronic acid due to fracture prevention, ranging from approximately -$74 for romosozumab versus zoledronic acid to approximately -$4,797 for abaloparatide versus zoledronic acid. These cost savings from prevention of fractures offset only a small portion of the anabolic drug costs. Romosozumab in particular showed little incremental effectiveness over zoledronic acid based on NMA results, thus the small incremental QALY denominator led to the largest incremental cost-effectiveness ratio among the anabolic therapies. The benefits to patients (measured in QALYs) resulted from small contributions across hip, clinical vertebral, and other fractures; however, because fracture events are relatively rare, most QALYs for each regimen are accrued by patients who remain in the "no new fracture" health state. In general, the modest clinical differences of the anabolic agents compared to zoledronic acid were not large enough to offset the cost increases. Probabilistic sensitivity analysis indicated that these results are highly uncertain, but in all cases the probability that the incremental cost-effectiveness ratios for the anabolic therapies were below $150,000 per QALY gained were quite low (abaloparatide: 7.7%; romosozumab: 0.4%; teriparatide: 0%). This was primarily due to the small QALY gains and higher prices of anabolics versus zoledronic acid.

One-Way Sensitivity Analyses

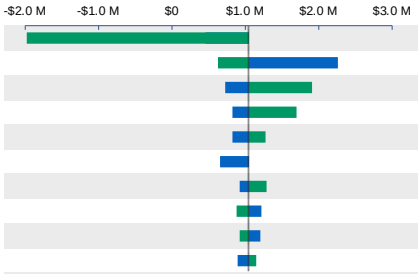
Detailed findings from the one-way sensitivity analyses can be found in Figures 5-7. In each one-way analysis, results were most sensitive to uncertainty in relative risk estimates for hip fracture, relative risk estimates for vertebral fracture, the long-term utility multipliers, and drug costs. Parameters associated with hip fractures were the largest contributors to uncertainty for abaloparatide and teriparatide versus zoledronic acid, particularly the anabolics' relative risks for hip fracture (the most expensive and severe of the fracture types) as they approached 1.0 (i.e., no

efficacy versus untreated patients). Uncertainty in the results for romosozumab versus zoledronic acid was associated with parameters specific to vertebral fracture and other fracture; however, the resultant incremental cost-effectiveness ratios were highly variable due to similar efficacy inputs for romosozumab and zoledronic acid in all three fracture types, leading to very small positive or negative incremental QALYs in the model.

Figure 5. Incremental Cost-Effectiveness Results of One-Way Sensitivity Analyses for Abaloparatide vs. Zoledronic Acid

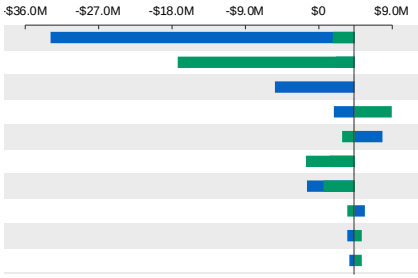
Parameter	Low Value	High Value	Low Result	High Result	Spread
Abaloparatide Relative Risk: Hip Fracture	0.300	0.910	$164,843	$4,938,998	$4,774,155
Utility Multiplier: Hip Fracture Year 2+	0.640	0.960	$218,228	$498,603	$280,375
Zoledronic Acid Relative Risk: Hip Fracture	0.670	0.930	$431,972	$218,370	$213,602
Abaloparatide Relative Risk: Vertebral Fracture	0.040	0.360	$264,005	$436,022	$172,017
Cost/pen: Abaloparatide	$949	$1,424	$229,736	$377,431	$147,696
Utility Multiplier: Vertebral Fracture Year 2+	0.745	1.000	$223,950	$349,658	$125,707
Utility Multiplier: Other Fracture Year 2+	0.800	1.000	$205,729	$303,584	$97,854
Abaloparatide Relative Risk: Other Fracture	0.300	0.910	$276,122	$356,325	$80,203
General Population Utility: Age 80+	0.576	0.864	$345,325	$270,845	$74,481
Utility Multiplier: Other Fracture Year 1	0.722	1.000	$269,029	$326,355	$57,326

Figure 6. Incremental Cost-Effectiveness Results of One-Way Sensitivity Analyses for Teriparatide vs. Zoledronic Acid



Parameter	Low Value	High Value	Low Result	High Result	Spread
Teriparatide Relative Risk: Hip Fracture	0.430	0.980	$462,823	-$1,979,393	$2,442,217
Zoledronic Acid Relative Risk: Hip Fracture	0.670	0.930	$2,269,118	$631,879	$1,637,239
Utility Multiplier: Hip Fracture Year 2+	0.640	0.960	$726,777	$1,909,440	$1,182,663
Teriparatide Relative Risk: Vertebral Fracture	0.180	0.430	$829,427	$1,705,331	$875,905
Cost: Teriparatide 600 mcg/2.4mL pen	$1,303	$1,954	$827,471	$1,278,177	$450,706
Utility Multiplier: Other Fracture Year 2+	0.800	1.000	$657,599	$1,052,824	$395,225
Teriparatide Relative Risk: Other Fracture	0.430	0.980	$931,488	$1,290,499	$359,011
Zoledronic Acid Relative Risk: Vertebral Fracture	0.230	0.370	$1,221,164	$891,726	$329,438
General Population Utility: Age 80+	0.576	0.864	$1,214,844	$928,935	$285,909
Utility Multiplier: Other Fracture Year 1	0.722	1.000	$905,434	$1,154,958	$249,524

Figure 7. Incremental Cost-Effectiveness Results of One-Way Sensitivity Analyses for Romosozumab vs. Zoledronic Acid



Parameter	Low Value	High Value	Low Result	High Result	Spread
Zoledronic Acid Relative Risk: Vertebral Fracture	0.230	0.370	-$32,796,153	$1,760,806	$34,556,959
Romosozumab Relative Risk: Other Fracture	0.540	1.140	$2,129,219	-$17,279,065	$19,408,284
Utility Multiplier: Other Fracture Year 2+	0.800	1.000	-$5,367,131	$4,388,095	$9,755,226
Utility Multiplier: Vertebral Fracture Year 2+	0.745	1.000	$1,842,192	$8,994,308	$7,152,116
Bisph Relative Risk: Other Fracture	0.670	0.930	$7,818,648	$2,876,278	$4,942,370
Romosozumab Relative Risk: Vertebral Fracture	0.160	0.470	$1,349,405	-$1,560,917	$2,910,322
Zoledronic Acid Relative Risk: Hip Fracture	0.670	0.930	-$1,416,926	$674,095	$2,091,021
Proportion of Clinical Vertebral Fractures	0.280	0.420	$5,667,959	$3,578,373	$2,089,586
Cost/month: Romosozumab	$1,303	$1,954	$3,504,691	$5,271,499	$1,766,807
Utility Multiplier: Vertebral Fracture Year 1	0.472	0.708	$3,730,174	$5,327,803	$1,597,629

Scenario Analyses

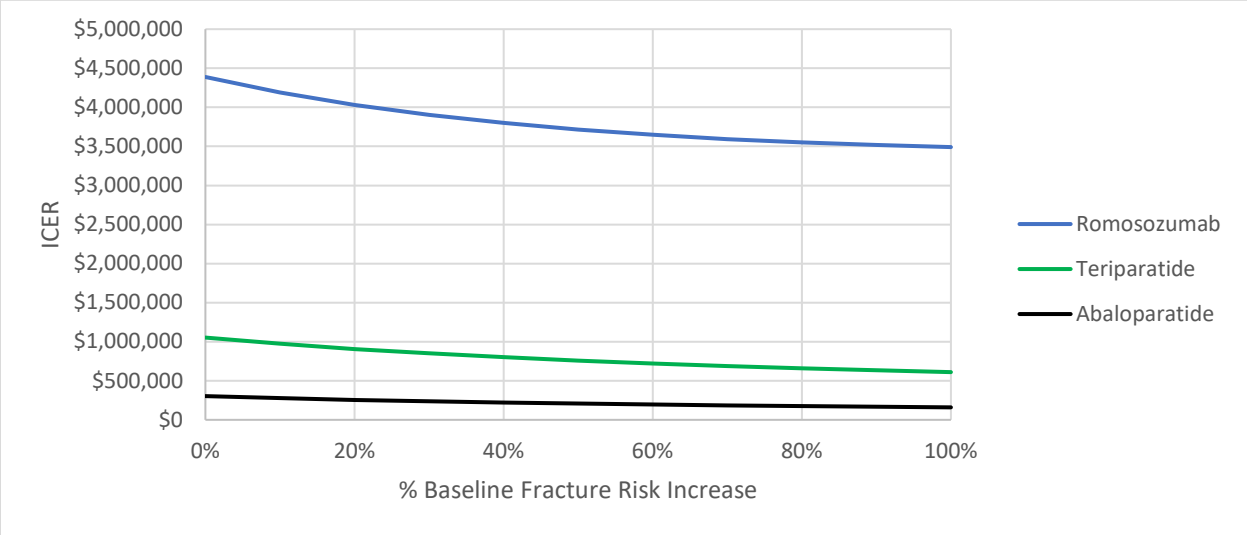
Below, we report the results of the most relevant or influential scenario analyses. Results from the scenario analyses pertaining to treatment efficacy ramp-up, maintenance, and rates of decline did

not yield major differences in conclusions from the base case and can be found in Appendix Figures F1-F3 and Tables F3-F6. In general, because efficacy maintenance was tied to the use of post-anabolic zoledronic acid, and because assumptions about zoledronic acid in both the baseline comparator arm and the anabolic arms were similar, changes in these parameters tended to impact all four arms similarly; thus, the small incremental QALY differences between anabolic drugs and zoledronic acid were relatively consistent with each scenario iteration. None of these scenarios produced a large enough QALY difference to lower the ICER below $150,000 per QALY.

Higher-Risk Group

To model patient populations with a higher risk of fracture than in the base-case, which was derived from the key clinical trials, a historical cohort,[57] and the online FRAX tool[14] we increased the age-dependent baseline fracture risks up to 100% of their base case value. The corresponding incremental cost-effectiveness ratios for each anabolic treatment in such higher-risk patient populations is shown in Figure 8 below. Fracture risks must be approximately 150% higher for abaloparatide to approach the $150,000 per QALY threshold, or the approximate risk of an 85-year-old woman with a T-score of -4. Romosozumab and teriparatide did not approach commonly-cited cost-effectiveness thresholds even at 1,000% increased risk of fracture.

Figure 8. Results of Higher Baseline Fracture Risk Scenario Analysis



Comparisons to No Treatment

We also considered a scenario in which patients may not be able to take zoledronic acid, and thus the comparator is no treatment. To do this, we compared the anabolics to a baseline fracture risk population (i.e. no relative risks were applied to baseline fracture estimates), and assumed the anabolic-treated patients did not receive zoledronic acid or its efficacy maintenance benefits

following initial anabolic therapy. We assumed anabolic efficacy linearly declined to 1.0 (i.e. no efficacy vs. placebo) over 3 years in the absence of zoledronic acid. The results for this scenario are shown below in Tables 17 and 18. In this scenario, incremental QALYs decreased due to the shortened efficacy time window for the anabolics, and none of the treatments reached the $150,000 per QALY threshold. None of the comparators approached commonly-cited cost-effectiveness thresholds when we varied our assumption of the number of years of efficacy decline from 3 years up to 10 years (as in the base case analysis).

Table 17. Results of Scenario Analysis Comparing Anabolic Drugs to No Treatment

Regimen	Cost	QALYs	Life Years
No Treatment	$21,404	8.867	12.1988
Romosozumab	$39,454	8.875	12.1989
Abaloparatide*	$46,736	8.892	12.1990
Teriparatide	$60,607	8.886	12.1990

*Assuming a 27% discount from WAC for abaloparatide
QALY: quality-adjusted life year

Table 18. Pairwise Results of Anabolic Drugs Compared to No Treatment

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. No Treatment
Romosozumab	$18,051	0.008	0.0001	$2,297,881
Abaloparatide*	$25,333	0.024	0.0002	$1,034,244
Teriparatide	$39,204	0.019	0.0002	$2,031,138

*Assuming a 27% discount from WAC for abaloparatide
Incr.: incremental, LY: life year, QALY: quality-adjusted life year

Increased Refracture Risk

As noted earlier, the baseline fracture risks reflect a mixed population of people with and without a prior fracture, so are higher than for someone who has never had a fracture but somewhat lower than for someone who has. In this scenario analysis, we further increased the refracture risk from baseline, using published estimates (Table 19)[74] to explore the impact on model results.

Table 19. Relative Risk of Subsequent Fracture for Scenario Analysis of Increased Refracture Risk

Model Input	Default	Lower	Upper	Distribution	Source
Post-Hip Fracture RR: Hip Fracture	2.30	1.20	3.40	Log-Normal	Klotzbuecher[74]
Post-Vertebral Fracture RR: Hip Fracture	2.30	1.84	2.70	Log-Normal	Klotzbuecher
Post-Vertebral Fracture RR: Vertebral Fracture	4.40	3.52	5.30	Log-Normal	Klotzbuecher
Post-Other Fracture RR: Hip Fracture	1.90	1.52	2.20	Log-Normal	Klotzbuecher
Post-Other Fracture RR: Vertebral Fracture	1.70	1.36	2.05	Log-Normal	Klotzbuecher
Post-Other Fracture RR: Other Fracture	3.30	2.64	4.05	Log-Normal	Klotzbuecher

Increasing refracture risks impacted the results by slightly amplifying the differences in relative risk parameters between the anabolic agents and zoledronic acid, resulting in modest improvements in incremental QALYs and cost (Table 21); however, none of these improvements were sufficient to make the incremental cost-effectiveness ratios for anabolic agents fall below $150,000 per QALY.

Table 20. Results When Including Increased Refracture Risk

Regimen	Cost	QALYs	Life Years
Zoledronic Acid	$21,463	8.902	12.192
Romosozumab	$40,610	8.909	12.192
Teriparatide	$59,112	8.950	12.198
Abaloparatide	$42,441	9.001	12.202

QALY: quality-adjusted life year

Table 21. Pairwise Results of Anabolic Drugs Compared to Zoledronic Acid When Including Increased Refracture Risk

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Romosozumab	$19,148	0.007	0.000	$2,869,642
Teriparatide	$37,649	0.048	0.006	$787,881
Abaloparatide	$20,978	0.099	0.011	$211,377

Incr.: incremental, LY: life year, QALY: quality-adjusted life year

Hip Fracture Relative Risks Derived Separately from Other Fractures

The incidence of hip fractures in the anabolic studies was low (see section 4.3), which led to wide credible intervals in the results of ICER's NMA. Given the instability of these estimates, we did not use them in the base-case analysis but present their impact in the scenario analysis below. The hip fracture relative risks in all four arms (Table 22) were reduced compared to the base-case estimates, in which hip fracture relative risks were equivalent to non-vertebral fracture relative risks, most notably for abaloparatide, which saw the greatest change in relative risks compared to that of zoledronic acid. These reductions in hip fractures, the most costly and severe fracture type, led to an approximate doubling of QALY gains for anabolics versus zoledronic acid, and greatly improved the ICERs for all three anabolics, although romosozumab and teriparatide still did not fall below the commonly-cited cost-effectiveness threshold of $150,000 per QALY (Table 24).

Table 22. Hip Fracture Relative Risks Derived Separately from Other Fractures

Model Input	Default	Lower	Upper	Source
Abaloparatide Hip Fracture Relative Risk	0.06	0.00	1.87	NMA of Hip Fractures*
Romosozumab Hip Fracture Relative Risk	0.27	0.15	0.45	NMA of Hip Fractures*
Teriparatide Hip Fracture Relative Risk	0.32	0.04	1.35	NMA of Hip Fractures*
Zoledronic Acid Hip Fracture Relative Risk	0.65	0.52	0.78	NMA of Hip Fractures*

*See Appendix Table E8 for detailed results

Table 23. Results When Using Hip Fracture Relative Risks Derived Separately from Other Fractures

Regimen	Cost	QALYs	Life Years
Zoledronic Acid	$16,218	8.975	12.204
Romosozumab	$30,388	9.049	12.213
Teriparatide	$51,853	9.050	12.213
Abaloparatide	$33,924	9.118	12.219

QALY: quality-adjusted life year

Table 24. Pairwise Results When Using Hip Fracture Relative Risks Derived Separately from Other Fractures

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Romosozumab	$14,170	0.074	0.008	$192,074
Teriparatide	$35,635	0.075	0.009	$474,299
Abaloparatide	$17,706	0.143	0.014	$123,694

Incr.: incremental, LY: life year, QALY: quality-adjusted life year

Drug Price Threshold Analysis

Prices for each drug that would achieve commonly-cited cost-effectiveness thresholds ranging from $50,000 to $150,000 per QALY gained are presented in Table 25.

Table 25. Resulting Package Prices for Each Anabolic Therapy to Reach Cost per QALY Thresholds

Drug	Base-Case Cost	$50,000/QALY	$100,000/QALY	$150,000/QALY
Abaloparatide (cost per month)	$1,186.25*	$371.56	$532.20	$692.83
Romosozumab (cost per month)	$1,628.45†	$29.10	$47.53	$65.96
Teriparatide (cost per pen)	$1,628.45	$179.13	$251.39	$323.65

*Assuming a 27% discount from WAC for abaloparatide

†A price for romosozumab is not publicly available; base-case cost figures represent parity pricing with teriparatide.

QALY: quality-adjusted life year

6.4 Model Validation and Prior Published Evidence on Costs and Cost-Effectiveness

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model produced findings consistent with expectations. Three independent modelers tested the mathematical functions in the model as well as the therapy-specific inputs and corresponding outputs.

We also compared the ICER model to previously published models. We searched the literature to identify models that were similar to our own, with comparable populations, settings, perspective, and treatments.

One manufacturer-funded study by Tosteson et al., compared teriparatide with bisphosphonates and no therapy in postmenopausal women eligible for osteoporosis treatment.[75] Both the ICER and Tosteson model were structurally similar Markov models, with differences in the included therapies, modeled time-horizon, and certain model-specific inputs.

Teriparatide was the common intervention in both studies. The bisphosphonates in the Tosteson model did not include zoledronic acid, which was included in the ICER model. Costs and QALYs for teriparatide were higher in the ICER model compared to the Tosteson model ($56,298 and 8.989 vs. $20,800 and 6.608, respectively). Several key differences between the two models contributed to the differences in results. 1) The ICER model adopted a lifetime time horizon while the Tosteson model time horizon was 10 years. The additional time in the ICER model contributed to the greater number of QALYs accrued and additional therapy costs. When treatment was modeled over a 10-year time span (results not shown), the ICER model showed QALY results that were similar to those in the Tosteson model. 2) The costs of therapy have increased substantially over time, with an annual teriparatide cost of approximately $6,300 in the Tosteson model versus approximately $21,200 in the ICER model. Additionally, the ICER model included bisphosphonate therapy post-anabolic therapy, and assumed that the full anabolic treatment effect was maintained by zoledronic acid for up to nine years after cessation of anabolic therapy. The Tosteson model assumed no residual treatment efficacy after treatment was completed. 3) The fracture probabilities in the Tosteson model were higher compared to the ICER model. 4) The base-case utilities in the ICER model were lower than in the Tosteson model. Additionally, utility multipliers and costs associated with vertebral fractures were applied to only 35% of the patients in the ICER model cohort to mirror the proportion of these fractures that were clinically apparent in a retrospective cohort analysis. 5) When comparing health state costs, the first-year costs for hip fracture were higher and first-year costs for vertebral fractures were lower in the ICER model compared to the Tosteson model.

Subsequent-year fracture costs in the ICER model were higher. Furthermore, we calculated the cumulative lifetime risk of fracture compared to Tosteson et al., who calculated fracture risk over only a 10-year time horizon. The excess mortality inputs for hip fracture were similar in both studies, as the ICER inputs were derived from the Tosteson model.

Other US-based models that we reviewed compared treatments that were not included in our analysis, so we did not conduct in-depth comparisons between these models and our own.[72,76-80] We found one ex-US model by Murphy et al. that compared teriparatide to no treatment in Swedish osteoporosis patients who had a T-score of -3.0 or less.[81] This model, which was run over a lifetime horizon with six-month cycles, resulted in incremental cost-effectiveness ratios of €5,897 per QALY ($7,990 per QALY) in patients with historical as well as incident vertebral fracture, and an incremental cost-effectiveness ratio of €18,701 per QALY gained ($25,340 per QALY) in those with only incident vertebral fractures. Compared to our model, these incremental cost-effectiveness results were significantly lower. One of the key drivers of the differences in the results between the two models is drug costs. When converted to US dollars, the annual cost of teriparatide in the Murphy et al., model was $7,290 (using 2011 currency exchange rates), while in the ICER model it was $21,243. Another key difference between the two models is in the assumed relative risk reduction of fractures compared to no treatment (0.17 for vertebral fractures and 0.47 for non-vertebral in Murphy et al. vs. 0.28 and 0.65, respectively, in the ICER model), This and other differences in the models resulted in a greater incremental QALY gain in the Murphy et al. analysis compared to the ICER model (0.189 vs. 0.019 QALYs).

7. Value-Based Benchmark Prices

Value-based benchmark prices will be released in the revised Evidence Report, which will be released on or about June 16, 2017.

8. Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of two new treatments for postmenopausal women with osteoporosis and high risk of fracture: abaloparatide and romosozumab. As romosozumab has not yet been approved by the FDA, its price is currently unknown. We therefore used the prices required to achieve the commonly-cited cost-effectiveness thresholds of $50,000, $100,000 and $150,000 per QALY in our estimates of budget impact. For abaloparatide, we used the WAC, an estimate of discounted WAC, and the three threshold prices in our estimates of budget impact. We did not include the other therapies modeled above in this analysis, given their established presence in the market.

Potential Budget Impact Model: Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapies.

The potential budget impact analysis included the entire candidate population for treatment, which consisted of postmenopausal women (assumed to be women over 50 years of age) diagnosed with osteoporosis and with a high risk of fractures. To estimate the size of the potential candidate population for treatment with abaloparatide or romosozumab, we first determined the number of women over 50 years of age in the US, approximately 62.6 million. Of those women, we assumed that 13% currently receive treatments for osteoporosis, based on a claims database analysis by Parthan et al., conducted to identify this percentage for a published budgetary impact analysis of denosumab in a hypothetical health plan.[82] Of those receiving treatment, 66% were diagnosed with osteoporosis while the remaining were treated for osteopenia.[82] We assumed that 46% of those women diagnosed and treated for osteoporosis had a high risk of osteoporotic fractures, based on occurrence of previous fractures and/or intolerance to previous osteoporosis treatment.[82] This high-risk population was assumed to be eligible to receive treatment with abaloparatide or romosozumab. Applying these estimates to the projected 2017 US population resulted in an estimate of approximately 2.47 million eligible patients in the US.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug or device that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. We assumed that abaloparatide and romosozumab would each take market shares from teriparatide and zoledronic acid in a ratio of 80:20 (i.e., each of the new drugs would take 80% from teriparatide and 20% from zoledronic acid). We tested the potential budget impact of the two new drugs by assuming different unit price points for each (WAC, discounted WAC, and the three cost-effectiveness threshold prices for abaloparatide; and the three cost-effectiveness threshold prices for romosozumab) against the calculated discounted WAC for existing drugs.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 26.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 26. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	33.5	FDA, 2016
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

Potential Budget Impact Model: Results

Table 27 below illustrates the per-patient budget impact results in more detail. Costs for abaloparatide were calculated using the WAC, discounted WAC, and threshold prices, and calculated for romosozumab using threshold prices. The discounted WAC price of teriparatide, and average WAC price for generic zoledronic acid were used to calculate costs for those treatments.

When treating the eligible cohort with abaloparatide, the average potential budgetary impact (adjusted for differing periods of drug utilization and associated cost-offsets over the five-year period) resulted in cost-savings using the discounted WAC and across all three cost-effectiveness thresholds, ranging from approximately -$2,000 per patient using the discounted WAC price ($1,186.25), to approximately -$8,800 per patient using the price to achieve $50,000 per QALY ($372). However, the average potential budgetary impact when using the WAC for abaloparatide was an additional per-patient cost of approximately $1,600; at that price, approximately 46% of the eligible cohort could be treated before reaching the $915 million annual budget impact threshold. Treating the eligible cohort with romosozumab resulted in cost-savings across all three cost-effectiveness thresholds, ranging from approximately -$11,400 per patient using the price to achieve $150,000 per QALY ($66) to approximately -$11,600 per patient using the price to achieve $50,000 per QALY ($29).

Table 27. Per-Patient Budget Impact Calculation Over a Five-year Time Horizon

	Average Annual Per Patient Budget Impact				
	WAC	Discounted WAC	$150,000/QALY	$100,000/QALY	$50,000/QALY
Abaloparatide	$13,834	$10,173†	$6,054	$4,714	$3,373
Teriparatide + Zoledronic acid* (Discounted WAC Only)	"	$12,191	"	"	"
Difference	$1,643	-$2,019‡	-$6,137‡	-$7,477‡	-$8,818‡
Romosozumab	N/A	N/A	$796	$696	$596
Teriparatide + Zoledronic acid* (Discounted WAC Only)	"	$12,191	"	"	"
Difference	N/A	N/A	-$11,395‡	-$11,495‡	-$11,595‡

*Weighted in the ratio 80:20 for teriparatide:zoledronic acid

†Assuming a 27% discount from WAC for abaloparatide

‡Indicates cost-saving

N/A: not available, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

9. Summary and Comment: Long-Term Cost Effectiveness and Potential Budget Impact

We estimated the cost-effectiveness of anabolic treatments compared to zoledronic acid in patients with osteoporosis at high risk for fragility fractures. The cost per additional QALY was estimated to be above $150,000 per QALY for each anabolic agent, assuming parity pricing with teriparatide for romosozumab and a 40% and 27% discount on prices of teriparatide and abaloparatide, respectively. This finding remained over a wide range of sensitivity and scenario analyses. These included analyses of patients at even higher risk for fracture, assuming that the benefits of zoledronic acid ramp-up over time, and varying the rate of decline in benefit after treatment is stopped. The results were most sensitive to uncertainty in relative risk estimates for hip fracture, relative risk estimates for vertebral fracture, long-term fracture utility multipliers, and drug costs. When the anabolic agents are compared to no treatment, the results suggest that anabolic treatments would not produce cost-effectiveness ratios of less than $150,000 per QALY.

Our study has some limitations that are worth noting. First, our model assumes a fracture hierarchy that prevents patients from having a fracture classified as less severe than their last fracture. This likely underestimates the number of less severe fractures, and potentially overestimates impacts of hip fractures, which was the most severe fracture in the hierarchy. We mitigated the influence of hip fracture by conservatively utilizing the relative risks of non-vertebral fractures for hip fracture (vs. hip fracture-only estimates), and by calibrating our base-case hip fracture estimates to reflect those predicted by the FRAX Fracture Assessment Tool. Second, we did not consider adverse events given that anabolic regimens and zoledronic acid exhibited similar serious adverse event rates compared to placebo and to each other in their respective trials. These small event rate differences would have minimal impact on the results. Third, we assumed 100% adherence to all treatments, which would not occur in actual practice. Finally, the magnitude of our base-case cost and cost-effectiveness results for romosozumab is tied to our assumption of price parity with teriparatide, due to a lack of available pricing on this new agent. Despite this, one-way sensitivity analysis showed that drug prices were much less influential on results than differences in fracture prevention efficacy, and we provided threshold analysis results to offer insight into the drug prices that would make each agent cost-effective under traditional thresholds.

Finally, budget impact analyses for abaloparatide and romosozumab indicate that use of both agents in place of teriparatide+zoledronic acid are not likely to generate access or affordability alerts, as both agents generate cost savings when using prices to achieve cost-effectiveness thresholds of $150,000 per QALY or lower, and also when using the assumed discounted WAC for abaloparatide. The analyses indicated that abaloparatide would reach the $915 million annual

budget impact threshold only if approximately 46% of the eligible cohort were to be treated and no price discount was offered, both of which are extremely unlikely.

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This is the first CTAF review of anabolic therapies for the treatment of osteoporosis in postmenopausal women.

References

1. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2014;29(11):2520-2526.
2. United States. Public Health Service. Office of the Surgeon General. *Bone health and osteoporosis : a report of the Surgeon General.* Rockville, Md.: U.S. Dept. of Health and Human Services, Public Health Service, Office of the Surgeon General; 2004.
3. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2007;22(3):465-475.
4. Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2011;26(1):19-26.
5. Miller PD, Hattersley G, Riis BJ, et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. *Jama.* 2016;316(7):722-733.
6. Wright NC, Saag KG, Curtis JR, et al. Recent trends in hip fracture rates by race/ethnicity among older US adults. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2012;27(11):2325-2332.
7. Gillespie CW, Morin PE. Trends and Disparities in Osteoporosis Screening Among Women in the United States, 2008-2014. *Am J Med.* 2017;130(3):306-316.
8. Jha S, Wang Z, Laucis N, Bhattacharyya T. Trends in Media Reports, Oral Bisphosphonate Prescriptions, and Hip Fractures 1996-2012: An Ecological Analysis. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2015;30(12):2179-2187.
9. Karlsson L, Lundkvist J, Psachoulia E, Intorcia M, Strom O. Persistence with denosumab and persistence with oral bisphosphonates for the treatment of postmenopausal osteoporosis: a retrospective, observational study, and a meta-analysis. *Osteoporos Int.* 2015;26(10):2401-2411.
10. Modi A, Sajjan S, Insinga R, Weaver J, Lewiecki EM, Harris ST. Frequency of discontinuation of injectable osteoporosis therapies in US patients over 2 years. *Osteoporos Int.* 2017;28(4):1355-1363.
11. US Food and Drug Administration (FDA). Forteo (teriparatide [rDNA origin] injection) for subcutaneous use) label. 2012; https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021318s036lbl.pdf.
12. FDA Approves Radius Health's TYMLOS™ (abaloparatide), a Bone Building Agent for the Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture [press release]. April 28, 2017.
13. US Food and Drug Administration (FDA). Tymlos (abaloparatide) injection, for subcutaneous use: label. 2017; https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208743lbl.pdf.
14. Amgen and UCB Announce U.S. FDA Accepatance of Biologics License Application for Romosozumab [press release]. 2016.

15. National Osteoporosis Foundation. Bone Health Index Survey: Final Report - September 2016. 2016.
16. California Department of Health Care Services. Contract Drugs List. 2017; http://files.medi-cal.ca.gov/pubsdoco/manual/man_query.asp?wSearch=%28%23filename+drugscdl%2a.doc+OR+%23filename+drugscdl%2a.zip%29&wFLogo=Contract+Drugs+List&wFLogoH=52&wFLogoW=516&wAlt=Contract+Drugs+List&wPath=N. Accessed March 28, 2017.
17. Aetna. 2017 Prescription Drug Search. 2017; https://rxtools.aetnamedicare.com/PlanCompare/indeptools2017/Tools/FormularySearch/FormularySearch.aspx. Accessed March 29, 2017.
18. Anthem Blue Cross. Your Blue Cross MedicareRx (PDP) with Senior Rx Plus Plan: 2017 Part D Formulary (List of Covered Drugs). 2017; https://www11.anthem.com/ca/provider/f0/s0/t0/pw_e234971.pdf. Accessed March 29, 2017.
19. Blue Shield of California. Blue Shield Medicare Basic Plan (PDP): 2017 Formulary. 2017; https://fm.formularynavigator.com/MemberPages/pdf/2017Basic_9107_BS%20CA%20Two%20Column_2614.pdf. Accessed March 29, 2017.
20. Cigna HealthSpring. 2017 Cigna-Healthspring Rx Comprehensive Drug List (Formulary). 2017; https://www.cigna.com/iwov-resources/medicare-2017/docs/formulary-ea-pdp-a.pdf?WT.z_nav=medicare%2Fpart-d%2Fdrug-list-formulary%3BBody%3BEnglish. Accessed March 29, 2017.
21. Health Net. Pharmacy Information Overview. 2017; https://www.healthnet.com/portal/provider/content/iwc/provider/unprotected/pharmacy_info/book/pharmacy_information.action#drug_info_medicare_plansContent. Accessed March 29, 2017.
22. Humana. Provider Drug List Search. 2017; http://apps.humana.com/UnsecuredDrugListSearch/Search.aspx. Accessed March 30, 2017.
23. United Healthcare. 2017 Comprehensive Formulary (complete list of covered drugs): AARP MedicareRX Walgreens (PDP). 2017; https://www.uhcmedicaresolutions.com/alphadms/ovdms10g/groups/ov/@ov/@highrespdf/documents/highrespdf/4044271.pdf. Accessed March 29, 2017.
24. Aetna. Aetna Medicare Rx Saver (PDP). 2017; https://www.aetnamedicare.com/documents/individual/2017/formularies/PA_2017_17020AET_a1_EN.pdf. Accessed March 29, 2017.
25. Anthem Blue Cross. Prior Authorization Criteria. 2017; https://www11.anthem.com/ca/provider/f0/s0/t0/pw_e234981.pdf. Accessed March 29, 2017.
26. Blue Shield of California. Medicare Part D Coverage Criteria: Forteo (teriparatide). 2017; https://www.blueshieldca.com/sites/medicare/documents/PA_CY2017_FORTEO%20teriparatide_MCweb.pdf. Accessed March 29, 2017.
27. United Healthcare. Prior Authorization Criteria. 2017; https://www.uhcmedicaresolutions.com/online_documents/ovation/pdf/pdp/en/2017/Prior_Auth_PWAG_2017.pdf. Accessed March 29, 2017.
28. Cigna HealthSpring. 2017 Cigna-HealthSpring Prior Authorization Criteria. 2017; https://www.cigna.com/iwov-resources/medicare-2017/docs/prior-authorization-chs.pdf?WT.z_nav=medicare%2Fpart-d%2Fdrug-list-formulary%3BBody%3BCigna-HealthSpring%20Medicare%20Plans. Accessed March 29, 2017.
29. Humana. Forteo (teriparatide) Pharmacy Coverage Policy (Medicare and Puerto Rico). Vol 20172016.

30. Blue Shield of California. Medicare Part D Coverage Criteria: zoledronic acid (generic Reclast). 2017; https://www.blueshieldca.com/sites/medicare/documents/PA_CY2017_zoledronic%20acid%20(generic%20RECLAST)_MCweb.pdf. Accessed March 29, 2017.
31. Humana. Reclast (zoledronic acid) Pharmacy Coverage Policy (Medicare, Exchanges, Puerto Rico, Commercial). 2016.
32. Humana. Zometa (zoledronic acid) Pharmacy Coverage Policy (Medicare, Exchanges, Puerto Rico, Commercial). 2017.
33. Anthem Blue Cross. Select Drug List: Drug list - Four Tier Drug Plan. 2017; https://fm.formularynavigator.com/FBO/143/Select_4_Tier_CA_IND_PDF_05267CAMENABC.pdf. Accessed March 28, 2017.
34. Blue Shield of California. Blue Shield Standard Drug Formulary. 2017; https://fm.formularynavigator.com/MemberPages/pdf/CommercialStandard2017_Closed_10143_BS%20CA%20Standard_2810.pdf. Accessed March 28, 2017.
35. Blue Shield of California. Specialty Drug List for Standard Drug Formulary. 2017; https://www.blueshieldca.com/bsca/documents/pharmacy/Specialty_Drugs_List_Standard_Formulary.pdf. Accessed March 28, 2017.
36. Kaiser Permanente. 2017 California Marketplace Formulary. 2017; https://healthy.kaiserpermanente.org/static/health/pdfs/formulary/cal/2017_ca_marketplace_formulary.pdf. Accessed March 28, 2017.
37. Health Net. Prior Authorization Protocol: Forteo (teriparatide). 2016; https://www.healthnet.com/portal/common/content/iwc/common/unprotected/pharmacy_info/prior_auth_criteria.action#f. Accessed March 29, 2017.
38. Camacho PM, Petak SM, Binkley N, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS - 2016. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists.* 2016;22(Suppl 4):1-42.
39. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. *Journal of Bone and Mineral Research.* 2016;31(1):16-35.
40. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int.* 2014;25(10):2359-2381.
41. North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause (New York, NY).* 2010;17(1):25-54; quiz 55-26.
42. National Institute for Health and Care Excellence. Secondary prevention of fragility fractures in postmenopausal women. 2017; https://pathways.nice.org.uk/pathways/osteoporosis#content=view-node%3Anodes-secondary-prevention-of-fragility-fractures-in-postmenopausal-women. Accessed April 5, 2017.
43. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
44. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008). The Cochrane Collaboration; 2008.
45. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine.* 2009;151(4):264-269, w264.

46. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
47. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(7521):897-900.
48. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. *N Engl J Med.* 2016;375(16):1532-1543.
49. Neer RM, Arnaud CD, Zanchetta JR, 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):1434-1441.
50. Cosman F, Miller PD, Williams GC, et al. Eighteen Months of Treatment With Subcutaneous Abaloparatide Followed by 6 Months of Treatment With Alendronate in Postmenopausal Women With Osteoporosis: Results of the ACTIVExtend Trial. *Mayo Clinic proceedings.* 2017;92(2):200-210.
51. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med.* 2007;356(18):1809-1822.
52. Harvey NC, Kanis JA, Oden A, et al. FRAX and the effect of teriparatide on vertebral and non-vertebral fracture. *Osteoporos Int.* 2015;26(11):2677-2684.
53. Cosman F, Hattersley G, Hu MY, Williams GC, Fitzpatrick LA, Black DM. Effects of Abaloparatide-SC on Fractures and Bone Mineral Density in Subgroups of Postmenopausal Women With Osteoporosis and Varying Baseline Risk Factors. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2017;32(1):17-23.
54. Black DM, Bilezikian JP, Ensrud KE, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med.* 2005;353(6):555-565.
55. Cosman F, Nieves JW, Dempster DW. Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2017;32(2):198-202.
56. Si L, Winzenberg TM, Palmer AJ. A systematic review of models used in cost-effectiveness analyses of preventing osteoporotic fractures. *Osteoporos Int.* 2014;25(1):51-60.
57. Melton LJ, 3rd, Crowson CS, O'Fallon WM. Fracture incidence in Olmsted County, Minnesota: comparison of urban with rural rates and changes in urban rates over time. *Osteoporos Int.* 1999;9(1):29-37.
58. Center for Metabolic Bone Diseases. FRAX Fracture Risk Assessment Tool - Calculation Tool (US). https://www.shef.ac.uk/FRAX/tool.aspx?country=9. Accessed May 1, 2017.
59. Kanis JA, Johansson H, Oden A, Dawson-Hughes B, Melton LJ, 3rd, McCloskey EV. The effects of a FRAX revision for the USA. *Osteoporos Int.* 2010;21(1):35-40.
60. Centers for Disease Control and Prevention. United States Life Tables, 2008. https://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_03.pdf.
61. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-effectiveness in health and medicine.* Oxford University Press; 2016.
62. Aitken M, Kleinrock M, Pennente K, Lyle J, Nass D, Caskey L. *Medicines Use and Spending in the U.S.: A review of 2015 and Outlook to 2020.* Parsippany, NJ: QuintilesIMS;2016.
63. Tosteson AN, Gottlieb DJ, Radley DC, Fisher ES, Melton LJ, 3rd. Excess mortality following hip fracture: the role of underlying health status. *Osteoporos Int.* 2007;18(11):1463-1472.
64. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. *Medical decision making : an international journal of the Society for Medical Decision Making.* 2006;26(4):391-400.

65. Kanis JA, Johnell O, Oden A, et al. The risk and burden of vertebral fractures in Sweden. *Osteoporos Int.* 2004;15(1):20-26.
66. Oleksik A, Lips P, Dawson A, et al. Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2000;15(7):1384-1392.
67. Peasgood T, Herrmann K, Kanis JA, Brazier JE. An updated systematic review of Health State Utility Values for osteoporosis related conditions. *Osteoporos Int.* 2009;20(6):853-868.
68. Burstrom K, Johannesson M, Diderichsen F. A comparison of individual and social time trade-off values for health states in the general population. *Health policy (Amsterdam, Netherlands).* 2006;76(3):359-370.
69. Redbook Online. 2017.
70. SSR Health. US Brand Rx Net Price. 2016.
71. Radius Health. TYMLOS™ and 1q 2017 Financial Results Update. [Investor presentation]. 2017; http://edge.media-server.com/m/p/z5woypf3. Accessed 38.
72. Parthan A, Kruse M, Yurgin N, Huang J, Viswanathan HN, Taylor D. Cost effectiveness of denosumab versus oral bisphosphonates for postmenopausal osteoporosis in the US. *Applied health economics and health policy.* 2013;11(5):485-497.
73. Shi N, Foley K, Lenhart G, Badamgarav E. Direct healthcare costs of hip, vertebral, and non-hip, non-vertebral fractures. *Bone.* 2009;45(6):1084-1090.
74. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2000;15(4):721-739.
75. Tosteson AN, Burge RT, Marshall DA, Lindsay R. Therapies for treatment of osteoporosis in US women: cost-effectiveness and budget impact considerations. *The American journal of managed care.* 2008;14(9):605-615.
76. Ivergard M, Strom O, Borgstrom F, Burge RT, Tosteson AN, Kanis J. Identifying cost-effective treatment with raloxifene in postmenopausal women using risk algorithms for fractures and invasive breast cancer. *Bone.* 2010;47(5):966-974.
77. Lekander I, Borgstrom F, Strom O, Zethraeus N, Kanis JA. Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK--results based on the Women's Health Initiative randomised controlled trial. *Bone.* 2008;42(2):294-306.
78. Lekander I, Borgström F, Ström O, Zethraeus N, Kanis JA. Cost-Effectiveness of Hormone Therapy in the United States. *Journal of Women's Health.* 2009;18(10):1669-1677.
79. Pham AN, Datta SK, Weber TJ, Walter LC, Colon-Emeric CS. Cost-effectiveness of oral bisphosphonates for osteoporosis at different ages and levels of life expectancy. *Journal of the American Geriatrics Society.* 2011;59(9):1642-1649.
80. Salpeter SR, Buckley NS, Liu H, Salpeter EE. The cost-effectiveness of hormone therapy in younger and older postmenopausal women. *Am J Med.* 2009;122(1):42-52.e42.
81. Murphy DR, Smolen LJ, Klein TM, Klein RW. The cost effectiveness of teriparatide as a first-line treatment for glucocorticoid-induced and postmenopausal osteoporosis patients in Sweden. *BMC musculoskeletal disorders.* 2012;13:213.
82. Parthan A, Emptage N, Taylor D, et al. Budgetary impact analysis of denosumab in a US health plan. *American Journal of Pharmacy Benefits.* 2013;5(5):e129-e138.

83. Murad MH, Drake MT, Mullan RJ, et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *The Journal of clinical endocrinology and metabolism.* 2012;97(6):1871-1880.
84. Freemantle N, Cooper C, Diez-Perez A, et al. Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. *Osteoporos Int.* 2013;24(1):209-217.
85. Davis S, Martyn-St. James M, Sanderson J, et al. Bisphosphonates for preventing osteoporotic fragility fractures (including a partial update of NICE technology appraisal guidance 160 and 161). National Institute for Health and Care Excellence (NICE); 2015.
86. Zhang L, Pang Y, Shi Y, et al. Indirect comparison of teriparatide, denosumab, and oral bisphosphonates for the prevention of vertebral and nonvertebral fractures in postmenopausal women with osteoporosis. *Menopause (New York, NY).* 2015;22(9):1021-1025.
87. Yang XC, Deng ZH, Wen T, et al. Network Meta-Analysis of Pharmacological Agents for Osteoporosis Treatment and Fracture Prevention. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology.* 2016;40(3-4):781-795.
88. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. 2008.

APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).

	#	Checklist item
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. PubMed search, January 24, 2017

#1	((("teriparatide"[MeSH Terms] OR teriparatide) OR ("abaloparatide"[Supplementary Concept] OR abaloparatide OR "AMG 785"[Supplementary Concept] OR "AMG 785" OR "romosozumab"[All Fields])
#2	#1 AND ("osteoporosis"[All Fields] OR "osteoporosis"[MeSH Terms] OR "osteopenia"[All Fields])))))
#3	((("addresses"[Publication Type] OR "autobiography"[Publication Type] OR "bibliography"[Publication Type] OR "biography"[Publication Type] OR "book illustrations"[Publication Type] OR "case reports"[Publication Type] OR "classical article"[Publication Type] OR "clinical conference"[Publication Type] OR "clinical trial, phase i"[Publication Type] OR "collected works"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "dataset"[Publication Type] OR "dictionary"[Publication Type] OR "directory"[Publication Type] OR "duplicate publication"[Publication Type] OR "editorial"[Publication Type] OR "electronic supplementary materials"[Publication Type] OR "ephemera"[Publication Type] OR "evaluation studies"[Publication Type] OR "festschrift"[Publication Type] OR "government publications"[Publication Type] OR "guideline"[Publication Type] OR "historical article"[Publication Type] OR "interactive tutorial"[Publication Type] OR "interview"[Publication Type] OR "introductory journal article"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "periodical index"[Publication Type] OR "personal narratives"[Publication Type] OR "pictorial works"[Publication Type] OR "portraits"[Publication Type] OR "practice guideline"[Publication Type] OR "retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "review"[Publication Type] OR "video audio media"[Publication Type] OR "webcasts"[Publication Type]))))
#4	((((("clinical study"[Publication Type] OR "clinical trial"[Publication Type] OR "comparative study"[Publication Type] OR "meta analysis"[Publication Type] OR "observational study"[Publication Type]))))
#5	#2 AND #4
#6	#5 NOT #3

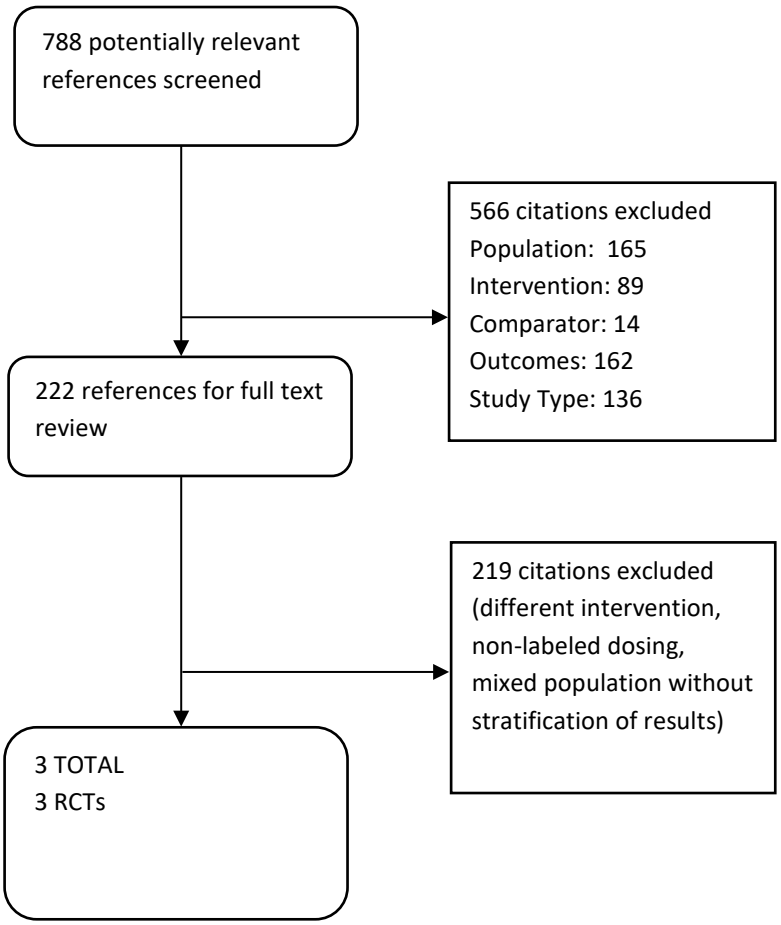
Table A3. Cochrane Central Register of Controlled Trials search, January 24, 2017 (via Ovid)

1	Exp teriparatide/
2	Teriparatide
3	Abaloparatide
4	Romosozumab
5	Osteopenia
6	Exp osteporosis
7	1 or 2 or 3 or 4
8	5 or 6
9	7 and 8

Table A4. Embase search, January 24, 2017

#1	'parathyroid hormone[1-34]'/exp OR 'parathyroid hormone[1-34]' OR 'teriparatide'/exp OR teriparatide OR 'forteo'/exp OR forteo OR 'abaloparatide'/exp OR 'abaloparatide' OR 'amg 785'/exp OR 'amg 785' OR 'romosozumab'/exp OR 'romosozumab' AND ('osteoporosis'/exp OR 'osteoporosis' OR 'osteopenia'/exp OR 'osteopenia')
#2	'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it
#3	#1 NOT #2
#4	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#5	'human'/exp
#6	#4 AND #5
#7	#4 NOT #6
#8	#3 NOT #7
#9	#8 AND [english]/lim
#10	#9 AND [medline]/lim
#11	#9 NOT #10
#12	#11 AND ('conference abstract'/it OR 'conference paper'/it)
#13	#11 NOT #12

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Anabolic Therapies for Osteoporosis



Appendix B. Public and Representative Private Insurer Coverage Policies

Table B1. Representative Medi-Cal and Silver-Tier Covered California Coverage Policies for Teriparatide, Alendronate, and Zoledronic Acid

	Medi-Cal	Anthem	Health Net	Kaiser Permanente	BSCA
Teriparatide					
Tier	Not listed	Non-formulary, Specialty	Specialty	4 (Specialty)	Specialty
ST	-	No	No	No	No
PA	-	No	Yes	No	No
Alendronate					
Tier	Covered	1	1	1, 2	1
ST	-	No	No	No	No
PA	-	No	No	No	No
Zoledronic Acid					
Tier	Covered	4	N/C	1	N/C
ST	-	No	-	No	-
PA	-	Yes	-	No	-
N/C: not covered, PA: prior authorization, ST: step therapy					

Appendix C. Previous Systematic Reviews and Technology Assessments

Systematic reviews and meta-analyses that compared fracture outcomes for two or more drugs in postmenopausal women with osteoporosis are summarized below.

Murad et al., 2012[83]

Murad and colleagues performed a systematic review and network meta-analysis of drugs for women with postmenopausal osteoporosis using data from 116 randomized studies. Teriparatide, alendronate, zoledronic acid, risedronate, denosumab, and the combination of calcium and vitamin D all significantly reduced hip fractures. There was a significant reduction in vertebral fractures compared to placebo for teriparatide, alendronate, zoledronic acid, risedronate, denosumab, ibandronate, and raloxifene. Similarly, there was a significant reduction in non-vertebral fractures compared to placebo for teriparatide, alendronate, zoledronic acid, risedronate, and denosumab. Teriparatide consistently had the highest probability of being ranked as the most effective, but was not significantly more effective than the other agents.

Fremantle et al., 2013[84]

Fremantle and colleagues performed a systematic review and network meta-analysis of therapies for osteoporosis using data from 34 randomized studies. They found that all agents significantly reduced the risk of vertebral fractures compared to placebo, alendronate and teriparatide significantly reduced non-vertebral fractures, and zoledronic acid, denosumab, and risedronate significantly reduced the risk for non-vertebral and hip fractures.

NICE, 2015[85]

David and colleagues performed a systematic review and network meta-analysis of bisphosphonate therapies for osteoporosis using data from the 27 of 46 randomized studies with fracture data. They found that all agents significantly reduced the risk of vertebral fractures compared to placebo and that there were no significant pairwise differences between active therapies. Zoledronic acid had the greatest effect on vertebral fracture rate reduction and increase in bone mineral density.

Zhang et al., 2015[86]

Zhang and colleagues performed a systematic review and network meta-analysis of teriparatide, denosumab, and oral bisphosphonates for women with postmenopausal osteoporosis using data from 15 randomized studies. Zoledronic acid was not considered. The concluded that teriparatide,

denosumab, alendronate and risedronate were effective at reducing vertebral and non-vertebral fractures compared to placebo and that denosumab, alendronate and risedronate reduce the risk of hip fractures. There were no significant differences in head to head comparisons of the drugs.

Yang, 2016[87]

Yang and colleagues performed a systematic review and network meta-analysis of drugs for women with postmenopausal osteoporosis using data from 36 randomized studies. Patients treated with alendronate, denosumab, and teriparatide had significantly lower rates of non-vertebral fractures than placebo. Alendronate, zoledronic acid, and denosumab were associated with a significantly lower risk of hip fractures compared to placebo. They did not consider vertebral fractures in their analysis.

Appendix D. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Abaloparatide					
Twenty-Four Month Extension Study of BA058-05-003 (ACTIVExtend) **NCT01657162**	Open-label extension trial	Alendronate (following 24 months of abaloparatide treatment in ACTIVE trial)	N = 1,200 Women only Patients enrolled and randomized to abaloparatide or placebo arm of ACTIVE trial No participants who withdrew from ACTIVE trial No participants with serious adverse events during ACTIVE trial	Incidence and severity of adverse events, fractures, and changes in laboratory values	October 2016 A 6-month pre-planned interim analysis has been published[50]

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Teriparatide					
VERtebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) **NCT01709110**	RCT	Teriparatide 20 mcg once daily, weekly oral placebo, daily calcium and vitamin D Risedronate 35 mg once weekly, daily placebo injection, daily calcium and vitamin D	N = 1,327 Ages 45 and older Postmenopausal women only BMD ≤ -1.5 At least 2 moderate or 1 severe vertebral fragility fractures No increased risk of osteosarcoma No history of unresolved skeletal disease that affect bone metabolism No history of atypical femoral fractures No abnormally high/low calcium levels No abnormally high parathyroid hormone levels No severe vitamin D deficiency No abnormal, uncorrected thyroid function No malignant neoplasms in previous 5 years No active liver disease, jaundice No significant impairment of hepatic/renal function No history of nephro/urolithiasis No previous/planned kypho/vertebroplasty No current or risk of osteonecrosis of the jaw No active or recent upper gastrointestinal disorders No inability to stand/sit upright for at least 30 minutes	Proportion of patients with new vertebral fractures at 24 months	July 2016 (study completed, but not yet published)

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Romosozumab					
Study to Determine the Efficacy and Safety of Romosozumab in the Treatment of Postmenopausal Women With Osteoporosis **NCT01631214**	RCT	Romosozumab and placebo alendronate for 12 months, then open-label alendronate for 12+ months Alendronate and placebo romosozumab for 12 months, then open-label alendronate for 12+ months	N = 4,093 Ages 55-90 Postmenopausal women only Hip BMD T-score of ≤ -2.5 and a vertebral fracture or hip BMD T-score of ≤ -2.0 and a recent hip fracture or two vertebral fractures No history of metabolic/bone disease other than osteoporosis No use of agents that affect bone metabolism No vitamin D insufficiency No prior solid organ or bone marrow transplant No hypo/hypercalcemia No hypo/hyperthyroidism No hypo/hyperparathyroidism No intolerance to alendronate	Incidence of clinical fracture at 24 months Incidence of new vertebral fracture at 24 months	November 2017

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix E. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[88] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Table E1. Summary of the Randomized Trials of Anabolic Agents for Osteoporosis

Reference	Study	Group	N	F/U (months)	T-score	Prior Fracture
Teriparatide						
Neer 2001[49]	Fracture Prevention Trial	Teriparatide 20 mcg SC QD Placebo SC QD	541 544	21	-	100% vertebral
Abaloparatide						
Miller 2016[5]	ACTIVE	Abaloparatide 80 mcg SC QD Teriparatide 20 mcg SC QD Placebo SC QD	824 818 821	18	-2.5 to -5.0	63% any 24% vertebral
Romosozumab						
Cosman 2016[48]	FRAME	Romosozumab 210 mg SC Qmo Placebo SC Qmo	3589 3591	12	-2.5 to -3.5	18% vertebral 22% non-vertebral
Key comparator: Zoledronic acid						
Black 2007[51]	HORIZON	Zoledronic acid 5 mg IV Q year Placebo IV Q year	3889 3876	36	-2.5 or lower	63% vertebral

F/U: follow-up, QD: once daily; Qmo: once monthly, Q year: once yearly

Table E2. Inclusion/Exclusion Criteria for the Randomized Trials of Anabolic Agents for Osteoporosis

Reference	Study	Inclusion	Exclusion	Co-intervention
Teriparatide				
Neer 2001[49]	Fracture Prevention Trial	Female 5+ years postmenopausal ≥ 1 moderate or 2 mild V Fx If ≤1 moderate V Fx, then additionally T-score < -1.0	Illnesses that affect bone Kidney stone in past 5 years Cr > 2.0 mg/dL Liver disease Substance abuse Recent use of drugs for osteoporosis	Vitamin D 400-1200 IU daily Calcium 1000 mg daily
Abaloparatide				
Miller 2016[5]	ACTIVE	Female Postmenopausal Ages 49-86 years T-score -2.5 to -5.0 ≥ 1 moderate or 2 mild V Fx or other fragility fracture in past 5 years Women ≥ 65 years with fracture eligible if T-score ≤ - 2.0 and > -5.0 Women ≥ 65 years without fracture if T-score ≤ - 3.0 and > -5.0 Normal serum calcium, PTH, phosphorus, alkaline phosphatase, and vitamin D levels	More than 4 V Fx Illnesses that affect bone Recent use of drugs for osteoporosis	None
Romosozumab				
Cosman 2016[48]	FRAME	Female Postmenopausal Ages 55-90 years T-score -2.5 to -3.5 Normal serum calcium, PTH, phosphorus, alkaline phosphatase, and 25(OH) vitamin D levels	Hip fracture Severe or >2 moderate V Fx Illnesses that affect bone ONJ Low vitamin D Recent use of drugs for osteoporosis	None
Key comparator: Zoledronic acid				
Black 2007[51]	HORIZON			
Cr: creatinine, ONJ: osteonecrosis of the jaw, PTH: parathyroid hormone, V Fx: vertebral fracture				

Table E3. Baseline Characteristics of Patients in Randomized Trials of Anabolic Agents for Osteoporosis

Reference	Group	Age	%F	% W	BMI, kg/m^2	Current Smoker, %	Prior treatment, %	BMD, mg/cm^2 L-Spine	Prior V Fx, n
Teriparatide									
Neer 2001[49]	Teriparatide	69	100	99	26.8	15.8	16	820	2.3
	Placebo	69	100	99	26.7	18.5	15	820	2.3
Abaloparatide									
Miller 2016[5]	Abaloparatide	69	100	80	25.0	NR	NR	829	NR
	Teriparatide	69	100	79	25.2	NR	NR	831	NR
	Placebo	69	100	80	25.1	NR	NR	823	NR
Romosozumab									
Cosman 2016[48]	Romosozumab	71	100	NR	24.7	NR	NR	NR	NR
	Placebo	71	100	NR	24.7	NR	NR	NR	NR
Key comparator: Zoledronic acid									
Black 2007[51]	Zoledronic acid	73	100	NR	25.1	NR	59%	790	NR
	Placebo	73	100	NR	25.4	NR	59%	790	NR

BMD: bone mineral density, BMI: body mass index, F: female, W: white, V Fx: vertebral fractures

Table E4. Quality Assessment of the Included Randomized Trials of Anabolic Agents for Osteoporosis

Reference	Comparable Groups	Maintain comparability	Double blind	Measurements equal and valid	Clear definition of intervention	Key outcomes assessed	Analysis appropriate	Quality
Teriparatide								
Neer 2001[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Abaloparatide								
Miller 2016[5]	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Good vs. placebo
Romosozumab								
Cosman 2016[48]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Key comparator: Zoledronic acid								
Black 2007[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

*Open-label teriparatide, double-blind abaloparatide and placebo

Table E5. Risk for Fracture in the Randomized Trials of Anabolic Agents for Osteoporosis

Reference	Group	V Fx	Non-V Fx	Hip Fx	Wrist Fx	Major osteoporotic Fx	Clinical fracture
Teriparatide							
Neer 2001[49]	Teriparatide	22 (5.0%)	30 (6.2%)	1 (0.2%)	7 (1.3%)	NR	NR
21 months	Placebo	64 (14.3%)	14 (9.8%)	4 (0.7%)	13 (2.4%)		
Abaloparatide							
Miller 2016[5]	Abaloparatide	4 (0.6%)	18 (2.7%)	0 (0%)	7 (0.8%)	10 (1.5%)	27 (4.0%)
18 months	Teriparatide	6 (0.8%)	24 (3.3%)	0 (0%)	17 (2.1%	23 (3.1%)	35 (4.8%)
	Placebo	30 (4.2%)	33 (4.7%)	2 (0.2%)	15 (1.8%)	34 (6.2%)	49 (8.3%)
Romosozumab							
Cosman 2016[48]	Romosozumab	16 (0.5%)	56 (1.6%)	7 (0.2%)	NR	38 (1.1%)	58 (1.6%)
12 months	Placebo	59 (1.8%)	75 (2.1%)	13 (0.4%)		63 (1.8%)	90 (2.5%)
Key comparator: Zoledronic acid							
Black 2007[51]	Zoledronic acid	92 (3.3%)	292 (8.0%)	52 (1.4%)	NR	NR	308 (8.4%)
36 months	Placebo	310 (10.9%)	388 (10.7%)	88 (2.5%)			456 (12.8%)

NR: not reported, V Fx: vertebral fracture, Non-V Fx: non-vertebral, non-hip fractures

Table E6. Relative Risk for Fractures in the Randomized Trials of Anabolic Agents for Osteoporosis

Reference	Group	V Fx	Non-V Fx	Hip Fx	Major osteoporotic Fx	Clinical fracture
Teriparatide						
Neer 2001[49]	Teriparatide Placebo	0.35 (0.22-0.55) 1 (ref)	0.47 (0.25-0.88) 1 (ref)	NR 1 (ref)	NR 1 (ref)	NR 1 (ref)
Abaloparatide						
Miller 2016[5]	Abaloparatide Teriparatide Placebo	0.14 (0.05-0.39) 0.20 (0.08-0.47) 1 (ref)	0.57 (0.32-1.00) 0.72 (0.42-1.22) 1 (ref)	NR NR 1 (ref)	0.30 (0.15-0.61) 0.67 (0.39-1.14) 1 (ref)	0.57 (0.35-0.91) 0.71 (0.46-1.09) 1 (ref)
Romosozumab						
Cosman 2016[48]	Romosozumab Placebo	0.27 (0.16-0.47) 1 (ref)	0.75 (0.53-1.05) 1 (ref)	0.54 (0.22-1.35) 1 (ref)	0.60 (0.40-0.90) 1 (ref)	0.64 (0.46-0.89) 1 (ref)
Key comparator: Zoledronic acid						
Black 2007[51]	Zoledronic acid Placebo	0.30 (0.24-0.38) 1 (ref)	0.75 (0.64-0.87) 1 (ref)	0.59 (0.42-0.83) 1 (ref)	 NR	0.67 (0.58-0.77)

NR: not reported, ref: referent group, V Fx: vertebral fracture, Non-V Fx: non-vertebral, non-hip fractures

Table E7. Bone Mineral Density Outcomes in Randomized Trials of Anabolic Agents for Osteoporosis

Reference	Group	BMD L spine	BMD femoral neck	BMD total hip
Teriparatide				
Neer 2001[49] **21 months**	Teriparatide Placebo	+9.7% +1.1%	+2.8% -0.7%	+2.6% -1.0%
Abaloparatide				
Miller 2016[5] **18 months**	Abaloparatide Teriparatide Placebo	+11.2% +10.5% +0.6%	+3.6% +2.7% -0.4%	+4.2% +3.3% -0.1%
Romosozumab				
Cosman 2016[48] **12 months**	Romosozumab Placebo	13.3 % difference	5.9% difference	6.9% difference
Key comparator: Zoledronic acid				
Black 2007[51] **36 months**	Zoledronic acid Placebo	6.7% difference	5.1% difference	6.0% difference

BMD: bone mineral density, L spine: lumbar spine

Table E8. Network Meta-Analysis Results for the Relative Risk of Hip Fractures*

Abaloparatide (80 mcg)				
0.29 (0.00 – 17.56)	**Teriparatide (20 mcg)**			
0.10 (0.00 – 3.73)	0.33 (0.02 – 2.59)	**Romosozumab (210 mg)**		
0.09 (0.00 – 2.81)	0.29 (0.03 – 1.80)	0.89 (0.31 – 2.38)	**Zoledronic Acid (5 mg)**	
0.05 (0.00 – 1.66)	0.17 (0.01 – 1.01)	0.52 (0.19 – 1.30)	**0.58** **(0.41 – 0.83)**	**Placebo**

***Includes data from open-label teriparatide arm of the ACTIVE trial

Legend: The drugs are arranged from most effective (top left) to least effective (bottom right) based upon placebo comparisons. Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1

Table E9. Network Meta-Analysis Results for the Relative Risk of Vertebral Fractures, Excluding Open-Label Teriparatide Arm from ACTIVE Trial

Abaloparatide (80 mcg)				
0.47 (0.12 – 1.45)	**Romosozumab (210 mg)**			
0.46 (0.14 – 1.21)	0.95 (0.51 – 1.66)	**Zoledronic Acid (5 mg)**		
0.41 (0.11 – 1.17)	0.84 (0.40 – 1.74)	0.89 (0.52 – 1.55)	**Teriparatide (20 mcg)**	
0.13 (0.04 – 0.33)	**0.27 (0.15 – 0.47)**	**0.29 (0.23 – 0.36)**	**0.32 (0.19 – 0.54)**	**Placebo**

Legend: The drugs are arranged from most effective (top left) to least effective (bottom right) based upon placebo comparisons. Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1

Table E10. Network Meta-Analysis Results for the Relative Risk of Non-Vertebral Fractures, Excluding Open-Label Teriparatide Arm from ACTIVE Trial

Abaloparatide (80 mcg)				
0.81 (0.45 – 1.44)	**Teriparatide (20 mcg)**			
0.69 (0.38 – 1.17)	0.83 (0.54 – 1.26)	**Zoledronic Acid (5 mg)**		
0.66 (0.33 – 1.28)	0.81 (0.46 – 1.42)	0.99 (0.65 – 1.50)	**Romosozumab (210 mg)**	
0.54 (0.30 – 0.92)	**0.65 (0.44 – 0.98)**	**0.79 (0.67 – 0.93)**	0.80 (0.55 – 1.14)	**Placebo**

Legend: The drugs are arranged from most effective (top left) to least effective (bottom right) based upon placebo comparisons. Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain 1

Appendix F. Comparative Value Supplemental Information

Table F1. Detailed Results Per Regimen

	Zoledronic Acid		Abaloparatide		Romosozumab		Teriparatide	
	Deterministic	Credible Range (from PSA)	Deterministic	Credible Range (from PSA)	Deterministic	Credible Range (from PSA)	Deterministic	Credible Range (from PSA)
Total Cost	$17,851	($14,277-$22,533)	$40,522	($33,256-$48,099)	$37,100	($31,051-$44,448)	$56,298	($47,171-$66,147)
Anabolic Cost	--		$27,574	($22,065-$33,081)	$19,376	($15,516-$23,204)	$41,148	($33,034-$49,380)
Zoledronic Acid Cost	$1,036	($820-$1,243)	$930	($747-$1,110)	$983	($778-$1,179)	$930	($736-$1,116)
Hip Fracture Cost	$2,995	($2,080-$4,149)	$2,141	($1,204-$3,549)	$2,994	($1,865-$4,587)	$2,504	($1,524-$3,925)
Vert Fracture Cost	$859	($633-$1,133)	$473	($251-$933)	$758	($495-$1,154)	$738	($487-$1,091)
Other Fracture Cost	$2,926	($2,172-$3,882)	$2,238	($1,285-$3,641)	$2,968	($1,964-$4,404)	$2,498	($1,574-$3,784)
Post-Fracture Cost	$10,034	($7,177-$13,863)	$7,165	($4,089-$11,728)	$10,021	($6,572-$15,168)	$8,482	($5,361-$13,111)
Total QALYs	8.95	(7.96-10.52)	9.03	(7.63-10.24)	8.96	(7.96-10.54)	8.99	(7.99-10.57)
Pre-Fracture QALYs	5.89	(5.15-7.15)	6.82	(5.52-8.05)	5.96	(5.15-7.35)	6.27	(5.42-7.66)
Hip Fracture QALYs	0.07	(0.05-0.09)	0.05	(0.03-0.08)	0.07	(0.04-0.10)	0.06	(0.03-0.09)
Vert Fracture QALYs	0.14	(0.11-0.17)	0.08	(0.04-0.15)	0.12	(0.08-0.18)	0.12	(0.08-0.17)
Other Fracture QALYs	0.20	(0.14-0.27)	0.15	(0.09-0.25)	0.20	(0.13-0.31)	0.17	(0.10-0.26)
Post-Fracture QALYs	2.65	(2.22-3.19)	1.93	(1.36-2.61)	2.60	(2.08-3.30)	2.37	(1.88-3.04)
Hip Fractures	0.17	(0.13-0.22)	0.12	(0.07-0.19)	0.17	(0.11-0.25)	0.14	(0.09-0.21)
Vert Fractures (all)	0.28	(0.24-0.34)	0.16	(0.09-0.29)	0.25	(0.18-0.36)	0.24	(0.17-0.34)
Other Fractures	0.37	(0.3-0.46)	0.29	(0.18-0.45)	0.37	(0.27-0.54)	0.32	(0.21 - 0.47)

Table F2. Detailed Incremental Results versus Zoledronic Acid

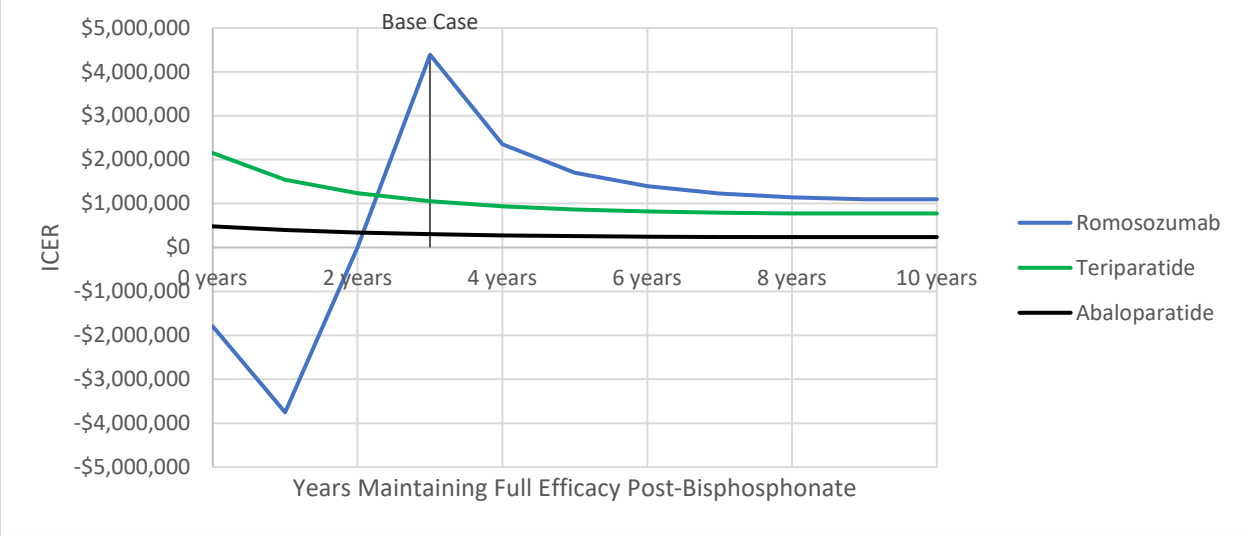
	Abaloparatide		Romosozumab		Teriparatide	
	Deterministic	Credible Range (from PSA)	Deterministic	Credible Range (from PSA)	Deterministic	Credible Range (from PSA)
ICER	$303,584	($82,518-$1,680,016)	$4,388,095	(-$11,261,480-$10,752,721)	$1,052,824	(-$9,607,285-$9,773,520)
Incremental Cost	$22,671	($15,744-$29,663)	$19,249	($13,784-$25,287)	$38,448	($29,523-$47,663)
Anabolic Cost	$27,574	($22,065-$33,081)	$19,376	($15,516-$23,204)	$41,148	($33,034-$49,380)
Zoledronic Acid Cost	-$106	(-$126--$85)	-$53	(-$64--$42)	-$106	(-$127--$84)
Hip Fracture Cost	-$854	(-$1,892-$279)	-$1	(-$874-$1,162)	-$492	(-$1,411-$573)
Vert Fracture Cost	-$386	(-$677-$57)	-$101	(-$375-$248)	-$122	(-$376-$181)
Other Fracture Cost	-$688	(-$1,717-$588)	$41	(-$920-$1,211)	-$428	(-$1,374-$668)
Post-Fracture Cost	-$2,869	(-$6,212-$732)	-$13	(-$2,893-$3,710)	-$1,553	(-$4,616-$1,867)
Incremental QALYs	0.07	(0.00-0.16)	0.00	(-0.07-0.06)	0.04	(-0.03-0.10)
Pre-Fracture QALYs	0.93	(0.20-1.61)	0.07	(-0.50-0.59)	0.38	(-0.19-0.91)
Hip Fracture QALYs	-0.02	(-0.04-0.01)	0.00	(-0.02-0.03)	-0.01	(-0.03-0.01)
Vert Fracture QALYs	-0.06	(-0.11-0.01)	-0.02	(-0.06-0.04)	-0.02	(-0.06-0.03)
Other Fracture QALYs	-0.05	(-0.12-0.04)	0.00	(-0.06-0.08)	-0.03	(-0.09-0.05)
Post-Fracture QALYs	-0.72	(-1.29--0.13)	-0.05	(-0.48-0.42)	-0.28	(-0.72-0.19)
Hip Fractures	-0.05	(-0.10-0.01)	0.00	(-0.05-0.06)	-0.03	(-0.08-0.03)
Vert Fractures	-0.12	(-0.20-0.01)	-0.03	(-0.12-0.07)	-0.04	(-0.12-0.05)
Other Fractures	-0.08	(-0.20-0.08)	0.01	(-0.11-0.15)	-0.05	(-0.17-0.09)

Supplemental Scenario Analyses

Years Maintaining Full Treatment Effect After Stopping Bisphosphonate Treatment

The base-case analyses assumed that the treatment effect of anabolic agents is maintained by follow-up treatment with zoledronic acid. Once zoledronic acid is stopped, we assumed the anabolic treatment effect is maintained for another three years before declining. Given the uncertainty in this assumption, we varied the duration of full treatment effect post-zoledronic acid from 0-10 years. Figure F1 shows how the incremental cost-effectiveness ratio of each anabolic treatment declines with longer duration of full treatment effect post-zoledronic acid treatment. The incremental cost-effectiveness ratios corresponding with the three-year post-bisphosphonate treatment reflect the base case scenario. Regardless of the assumed duration of effect, the incremental cost-effectiveness ratios did not approach $150K per QALY. As in the one-way sensitivity analysis results, romosozumab exhibited highly uncertain incremental cost-effectiveness ratios as incremental QALYs moved from small negative to small positive estimates.

Figure F1. Results of Anabolic Treatment Efficacy Maintenance Scenario Analysis

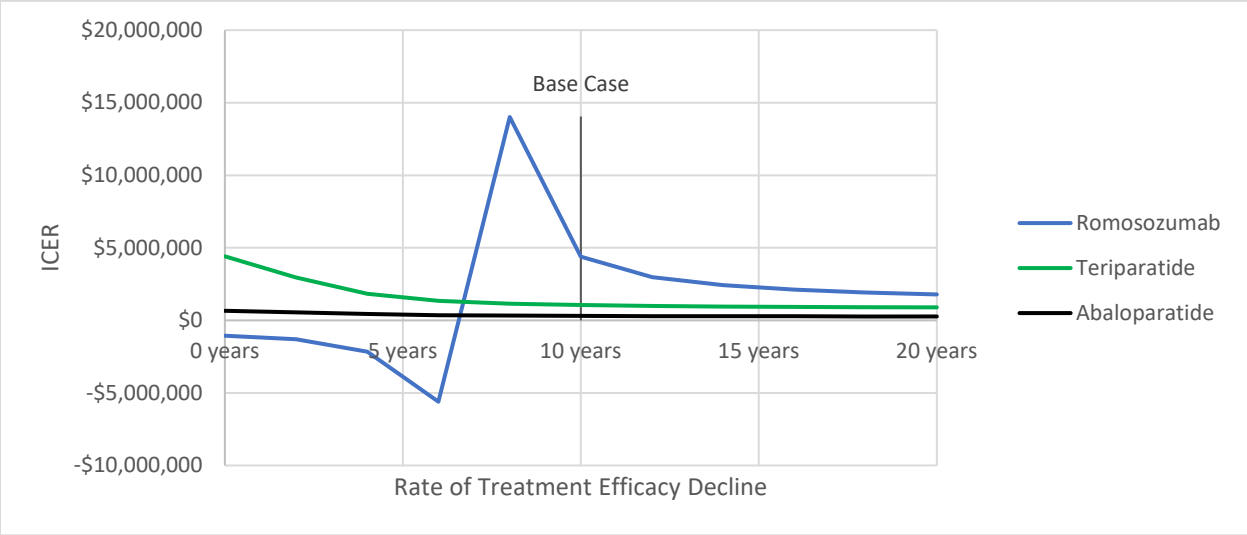


Rate of Treatment Effect Decline

Another key assumption was the rate of treatment effect decline over time once zoledronic acid therapy is stopped. Figure F2 below shows how the ICER for each anabolic treatment varied with the number of years it takes for the treatment effect to decline from full treatment effect to the baseline fracture rates, assuming the decline starts 3-years post-bisphosphonate treatment and declines linearly. The incremental cost-effectiveness ratios corresponding with the 10-year decline time reflect the base case scenario. Similar to the scenario analysis above, the ICERs stay well above the upper cost-effectiveness threshold of $150,000 per QALY. As in earlier sensitivity analysis

results, romosozumab exhibited irrational ICERs as incremental QALYs moved from negative to positive estimates.

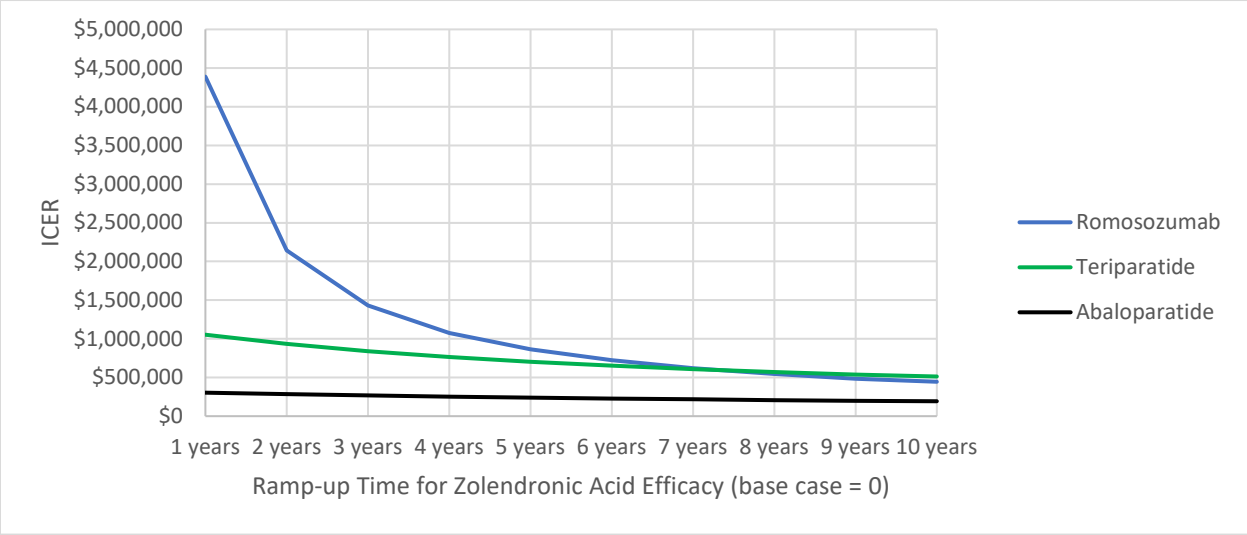
Figure F2. Efficacy Decline Duration Scenarios



Ramp-Up Time for Efficacy of Zoledronic Acid

We explored the impact of various assumptions regarding the rate at which zoledronic acid reaches full efficacy in the baseline comparator arm (Figure F3). All three anabolic regimens' incremental cost-effectiveness ratios improved the longer it took zoledronic acid to reach full efficacy, as expected. However, even with 10 years' ramp-up time for zoledronic acid, the anabolic agents did not reach the $150,000 per QALY threshold. The following scenario analysis, comparison of anabolics to no treatment, further explains this result.

Figure F3. Zoledronic Acid Ramp-Up Time Scenarios



Excluding Open-Label Teriparatide Data from ACTIVE Trial in NMA RR Estimates

The exclusion of the ACTIVE trial's teriparatide results in the NMA resulted in slightly different relative risk estimates for teriparatide and abaloparatide, presented below. This resulted in a small decline in incremental QALYs and slight cost increases for abaloparatide and teriparatide, which somewhat increased their ICERs.

Table F3. Model Inputs for Scenario Analysis Excluding Open-Label Teriparatide Data from ACTIVE Trial

Drug	Vertebral Fracture RR	Non-Vertebral Fracture RR*
Zoledronic Acid 5 mg	**0.29 (0.23 – 0.36)**	**0.79 (0.67 – 0.93)**
Abaloparatide 80 mcg	**0.13 (0.04 – 0.33)**	**0.54 (0.30 – 0.92)**
Romosozumab 210 mg	**0.27 (0.15 – 0.47)**	0.80 (0.55 – 1.14)
Teriparatide 20 mcg	**0.32 (0.19 – 0.54)**	**0.65 (0.44 – 0.98)**

*Non-vertebral fracture relative risks were used for hip fractures and other non-vertebral fractures
RR: relative risk

Table F4. Results of Scenario Analysis Excluding Open-Label Teriparatide Data

Regimen	Cost	QALYs	Life Years
Zoledronic Acid	$17,851	8.953	12.202
Romosozumab	$37,100	8.957	12.202
Teriparatide	$56,361	8.986	12.206
Abaloparatide	$40,671	9.026	12.208

QALY: quality-adjusted life year

Table F5. Pairwise Results of Anabolic Drugs Compared to Zoledronic Acid, Excluding Open-Label Teriparatide Data

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Abaloparatide	$22,820	0.074	0.006	$309,896
Teriparatide	$38,510	0.033	0.004	$1,175,644
Romosozumab	$19,249	0.004	0.000	$4,388,095

Incr.: incremental, LY: life year, QALY: quality-adjusted life year