Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value

Evidence Report

June 16, 2017

Prepared for

Note: When our process began, ICER expected FDA approval of two new anabolic agents for osteoporosis in the first half of 2017. On May 21, 2017, Amgen and UCB issued a press release with topline results from the ARCH trial of romosozumab. Among the findings summarized was a new safety signal regarding serious cardiovascular adverse events. Amgen has agreed with the FDA that the ARCH data should be considered in the regulatory review prior to the initial marketing authorization, and as a result the company does not expect approval of romosozumab in the US to occur in 2017.

Due to this delay, we have removed romosozumab from our network meta-analysis and our economic modeling and will not consider any voting questions that include romosozumab. However, we have elected to retain the summary of the romosozumab trial results as well as the newly available summary results of the ARCH trial because they provide important contextual information to frame the larger discussion of the role of anabolic therapies in preventing osteoporotic fractures.

ICER Staff and Consultants	University of Washington School of Pharmacy Modeling Group
Jeffrey A. Tice, MD Professor of Medicine University of California, San Francisco **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **Varun Kumar, MBBS, MPH, MSc** Health Economist Institute for Clinical and Economic Review **Patricia Synnott, MALD, MS** Senior Research Associate Institute for Clinical and Economic Review **Matt Seidner, BS** Program Manager Institute for Clinical and Economic Review **Daniel A. Ollendorf, PhD** Chief Scientific Officer Institute for Clinical and Economic Review **David M. Rind, MD, MSc** Chief Medical Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**Lotte Steuten, MsC, PhD** Associate Professor Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy University of Washington **Gregory F. Guzauskas, MSPH, PhD** Senior Research Scientist Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy University of Washington **David L. Veenstra, PharmD, PhD** Professor and Associate Director Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy University of Washington *The role of the University of Washington (UW) School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UW.*

DATE OF PUBLICATION: June 16, 2017

We would also like to thank Sonya Khan and Noah Mwandha for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at https://icer-review.org/programs/ctaf/.

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/

Expert Reviewers

Douglas Bauer, MD
Professor of Medicine
University of California, San Francisco School of Medicine
No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Teresa Fama, MD
Rheumatologist
University of Vermont Health Network, Central Vermont Medical Center
No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Anna N. A. Tosteson, ScD
James J Carroll Professor
Professor of Medicine and of The Dartmouth Institute for Health Policy and Clinical Practice
Director, Multidisciplinary Clinical Research Program in Musculoskeletal Diseases
Director, Comparative Effectiveness Research Program. The Dartmouth Institute for Health Policy and Clinical Practice
Geisel School of Medicine at Dartmouth
No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Table of Contents

List of Acronyms Used in this Report

ACE	American College of Endocrinology
ACP	American College of Physicians
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
HEDIS	Health Effectiveness Data and Information Set
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
PTHrP	Parathyroid hormone-related protein
QALY	Quality-adjusted life-year
QM	Quantitative morphometry
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
SQ	Semiquantitative
UHC	United Healthcare
US	United States
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

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.). 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 abaloparatide and teriparatide, because the FDA is no longer expected to issue a decision on romosozumab in 2017.[4]

The Topic in Context

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 approximately half of white women ages 75 and older have osteoporosis. Osteoporosis is also diagnosed when an individual experiences a fragility fracture in a location associated with osteoporosis (i.e., vertebra, hip). A fragility fracture is a fracture from a low-energy injury 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]

Many organizations have treatment guidelines for osteoporosis.[5-9] 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 may also be 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, less evidence of efficacy, route of administration, and/or cost.

Osteoporotic fractures can lead to pain, disability, and death. Even vertebral fractures that do not come to clinical attention may result in loss of height and pronounced curving of the spine (kyphosis) that interferes 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.[10] 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.[6]

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 estimate that only 45% of patients remain adherent with oral bisphosphonate therapy one year after the initial prescription and only 30% after two years.[11] 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.[12] This appears to be a problem across classes of parenteral agents for osteoporosis with discontinuation rates at one year of 49% for denosumab, 59% for zoledronic acid, and 67% for teriparatide.[12]

Given the poor adherence to currently available therapies, new treatments are needed. Individuals on currently-approved drugs 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) and PTH-related Protein (PTHrP) 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, 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.[13] Teriparatide requires a daily injection of 20 mcg under the skin and the drug must be kept refrigerated. Patients are supplied with a pen injector that contains 28 daily doses, which translates to approximately 13 pens per year. 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 PTHrP analog, approved by the FDA on 4/28/17.[14] 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.[15] Abaloparatide requires a daily injection of 80 mcg under the skin, but does not require refrigeration after the first dose. Abaloparatide is administered by a pen injector containing 30 daily doses, or approximately 12 pens per year.

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, and a decision in 2017 is no longer anticipated while the FDA reviews data from the ARCH trial that includes an unexpected safety signal regarding serious cardiovascular adverse events.[4]

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.[16] 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 with all of the anabolic therapies.

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.

Comparative Clinical Effectiveness

For each of the three anabolic drugs, there is only one pivotal trial.[17-19] Each of the trials is good quality and is described in detail in the full report. The pivotal trial of abaloparatide also included open-label teriparatide. We performed a network meta-analysis to compare each drug to the others and included zoledronic acid in the NMA based on feedback from multiple stakeholders. Guidelines recommend zoledronic acid for patients at high risk for fracture and it is a commonly used parenteral therapy for patients with osteoporosis who are unable to tolerate oral therapy. We performed NMAs for morphometric vertebral fractures (i.e., fractures identified by radiographic assessment of paired x-rays of the spine obtained before randomization and at the end of the trial) and non-vertebral fractures. There were insufficient data to evaluate hip fractures in an NMA. As noted above, we excluded romosozumab from all comparative effectiveness analyses including the NMAs.

The studies all enrolled postmenopausal women at high risk of fracture. However, the inclusion criteria were different and there were baseline differences in the percentage of participants within each trial with vertebral fractures at baseline (Table ES1 below). If there was significant effect modification for any of the drugs by vertebral fracture status (for example, if one of the drugs was more effective among women with prior fracture than no prior fracture), then it would be inappropriate to combine the studies in a network meta-analysis. However, investigators have specifically analyzed the clinical trials for each of the drugs for effect modification by prior vertebral fracture and other baseline measure and have not identified significant effect modification.

Table ES1. Summary of the Randomized Trials of Anabolic Agents and Zoledronic Acid for Osteoporosis

Reference	Study	Group	N	F/U, months	Age, years	BMI, kg/m^2	Prior Fracture
Neer 2001[19]	Fracture Prevention Trial	Teriparatide Placebo	541 544	21 21	69 69	26.8 26.7	100% V
Miller 2016[18]	ACTIVE	Abaloparatide Teriparatide Placebo	824 818 821	18 18	69 69	25.0 25.2 25.1	24% V 63% any
Cosman 2016[17]	FRAME	Romosozumab Placebo	3589 3591	12 12	71 71	24.7 24.7	18% V 22% non-V
Black 2007[20]	HORIZON	Zoledronic acid Placebo	3889 3876	36 36	73 73	25.1 25.4	63% V

Non-V: non-vertebral fracture, V: vertebral fracture

Clinical Benefits

Morphometric Vertebral Fractures

The pivotal trials of teriparatide, abaloparatide, and zoledronic acid all reported a significant reduction in vertebral fractures, though the definition of incident vertebral fractures differs somewhat between trials.[18-20] The results of the NMA confirmed this finding (Table ES2 below). For teriparatide, we used data from a re-analysis conducted by Prevhral et al in 2009, [21] eight years after the original trial. In the Prevhral analysis, the investigators assessed vertebral fractures using an approach that was similar to the one taken in the trials of abaloparatide and zoledronic acid (see full report for additional details); this definition resulted in a lower incidence of new vertebral fractures than in the original paper. All three drugs were significantly better than placebo at reducing morphometric vertebral fractures. Neither of the two anabolic agents was significantly different from one another, nor were they significantly different from zoledronic acid; the credible intervals for the three comparisons of the active drugs all contain 1.

Table ES2. Network Meta-Analysis Results for the Relative Risk of Morphometric Vertebral Fractures*

Abaloparatide (80 mcg)			
0.76 (0.20 – 2.26)	**Teriparatide (20 mcg)**		
0.44 (0.12 – 1.15)	0.57 (0.30 – 1.02)	**Zoledronic Acid (5 mg)**	
0.13 (0.03 – 0.33)	**0.17 (0.09 – 0.29)**	**0.30 (0.24 – 0.37)**	**Placebo**

Legend: Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.

As expected, the NMA estimates for the reduction in vertebral fractures for each drug versus placebo are similar to the direct estimates versus placebo in the randomized trials (Table ES3 below).

Table ES3. Comparison of the Relative Risk Versus Placebo for Morphometric Vertebral Fractures Between the Network Meta-Analysis and the Randomized Controlled Trials

Drug	NMA Estimate	RCT Estimates
Abaloparatide	0.13 (0.03-0.33)	0.14 (0.05-0.39)
Teriparatide	0.17 (0.09-0.29)	0.16 (0.08-0.33) 0.20 (0.08-0.47)
Zoledronic acid	0.30 (0.24-0.37)	0.30 (0.24-0.38)

Non-Vertebral Fragility Fractures

In the key randomized trials, both teriparatide and abaloparatide significantly reduced non-vertebral fractures. The results of the NMA confirmed this finding (Table ES4). Again, neither of the anabolic agents were significantly different from one another, nor were they significantly different from zoledronic acid.

Table ES4. Network Meta-Analysis Results for the Relative Risk of Non-Vertebral Fragility Fractures*

Abaloparatide (80 mcg)			
0.83 (0.46 – 1.46)	**Teriparatide (20 mcg)**		
0.69 (0.38 – 1.16)	0.82 (0.54 – 1.22)	**Zoledronic Acid (5 mg)**	
0.51 (0.28 – 0.85)	**0.61 (0.41 – 0.88)**	**0.75 (0.64 – 0.87)**	**Placebo**

Legend: Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.

As with vertebral fractures, the NMA estimates for the reduction in non-vertebral fractures for each drug versus placebo are similar to the direct estimates versus placebo in the randomized trials (Table ES5 below).

Table ES5. Comparison of the Relative Risk Versus Placebo for Non-Vertebral Fractures Between the Network Meta-Analysis and the Randomized Controlled Trials

Drug	NMA Estimate	RCT Estimates
Abaloparatide	0.51 (0.28-0.85)	0.57 (0.32-1.00)
Teriparatide	0.61 (0.41-0.88)	0.47 (0.25-0.88) 0.72 (0.42-1.22)
Zoledronic acid	0.75 (0.64-0.87)	0.75 (0.64-0.87)

Hip Fractures

Hip fractures are an important sub-type of non-vertebral fractures because they are associated with loss of independence and mortality in additional to significant short-term morbidity and costs. The randomized trials of abaloparatide and teriparatide did not have sufficient power to demonstrate a reduction in hip fractures, but one observational data reported a 45% reduction in hip fractures for teriparatide.[22] The randomized trial of zoledronic acid found a 41% reduction in hip fractures compared to placebo (RR 0.59, 95% CI 0.42-0.83).

Harms

In the pivotal trials, there were no significant differences in serious adverse events or discontinuation due to adverse events between the active treatments and placebo. Both abaloparatide and teriparatide are associated with injection site reactions and hypercalcemia. Rats developed osteosarcomas during treatment with abaloparatide and teriparatide, but this has not

been observed in humans. However, the treatment duration for the two drugs is limited to two years due to concerns that prolonged use could cause osteosarcomas. Zoledronic acid is associated with flu-like infusion reactions in up to 30% of patients following the first treatment.

Zoledronic acid has also been associated with rare, but serious atypical femoral fractures and osteonecrosis of the jaw. It is estimated that treatment of 10,000 women with zoledronic acid for 3 years would prevent approximately 710 vertebral fractures, 110 hip fractures, while causing 1 atypical femoral fracture and less than 1 case of osteonecrosis of the jaw.

Controversies and Uncertainties

The primary controversy is whether it was appropriate to combine the data from the different study populations of the three trials in a NMA. As noted earlier, there is evidence that there is no effect modification for any of the drugs by patient characteristics including prior vertebral fractures and other risk factors for fracture. Thus, it is appropriate to compare the relative effects of the drugs in a network meta-analysis.

None of the published NMAs of drug therapy for osteoporosis included abaloparatide (see Appendix C).[23-27] Similar to our findings, the NMAs concluded that both teriparatide and zoledronic acid reduce the risk of vertebral and non-vertebral fractures compared to placebo. They found no significant differences between the drugs, though teriparatide ranked higher than zoledronic acid. They also concluded that zoledronic acid reduced hip fractures, but there was insufficient evidence for teriparatide.

A major area of uncertainty reflects 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, 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. Indeed, the recent ACP clinical guideline did not recommend any of the anabolic agents as first line therapy for osteoporosis because of the lack of randomized trial evidence on hip fracture prevention.[9]

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. However, 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. 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). 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.[28] 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 previously treated with anti-resorptive drugs.[29] This suggests that anabolic agents may be most effective if used prior to anti-resorptive therapy. 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 two anabolic agents reduce vertebral fractures compared to no therapy. 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 both initial anabolic therapy and subsequent anti-resorptive therapy is essential to preserve the fracture reduction benefit. However, there are minimal real-world data available to compare adherence to therapy between the two anabolic agents.

For the two anabolic agents, we judged 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 non-vertebral fractures, and uncertain benefits for hip fractures, though observational data do support a benefit for teriparatide.

When abaloparatide is compared to teriparatide, we judged that there is insufficient evidence to assess the comparative clinical effectiveness of the two drugs because of low certainty in the evidence. The extensive real world clinical experience with teriparatide without identification of

new adverse events and observational evidence confirming benefits is reassuring. However, in the ACTIVE trial, there was a non-significant trend towards greater reduction in both vertebral and non-vertebral fractures with abaloparatide compared with teriparatide.

Other Benefits or Disadvantages

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. 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.

There are no clear differences among the anabolic drugs in terms of impact on caregiver burden, although daily injections may be burdensome if a caregiver is required to perform the injection.

Abaloparatide acts through a similar mechanism as teriparatide. However, both anabolic drugs work through a fundamentally different mechanism from the other available agents, including zoledronic acid. There is evidence that starting with an anabolic agent followed by an antiresorptive agent may result in greater long-term fracture prevention than treating with an antiresorptive agent for the same length of time. However, to date, there are no published randomized trials demonstrating that this is the optimal approach.

Comparative Value

We conducted a cost-effectiveness analysis using a simulation model comparing the anabolic drugs abaloparatide and teriparatide, each followed by treatment with a bisphosphonate (zoledronic acid), versus treatment with zoledronic acid alone in a representative cohort of postmenopausal women who are at high risk for osteoporotic fractures. The target population was 70-year-old postmenopausal women with a fracture incidence similar to that observed in the clinical trials of the anabolic drugs. Annual relative risks of vertebral and other non-vertebral fractures for each drug were obtained from our evidence review's NMA. Relative risk of hip fractures was estimated using the ratio of hip to non-vertebral fracture relative risks reported in the HORIZON trial (zoledronic acid vs. placebo). Briefly, the HORIZON-derived ratio was 0.59 (hip) / 0.75 (non-vertebral) = 0.79, which was multiplied by the NMA-derived relative risks for non-vertebral fractures (abaloparatide = 0.51, teriparatide = 0.61) to obtain base case estimates. Other estimates of relevant clinical parameters, quality of life measures, and drug and health care costs were obtained from published literature. The model tracks vertebral fractures (both morphometric and clinical), hip fractures, other non-vertebral fractures, and death. The model's base case analysis

adopted a health care system perspective with outcomes modeled over a life-time horizon using 3% discount rates for costs and outcomes.

The model evaluated the lifetime effect of two years of anabolic therapy with either abaloparatide or teriparatide followed by six years of treatment with zoledronic acid, and assumed 100% adherence and 100% efficacy for the full treatment period (i.e., eight years) plus an additional three years. Each anabolic agent was associated with a net price per pen based on the wholesale acquisition cost (WAC) of $2,998 for teriparatide and $1,625 for abaloparatide. We applied a discount of 38% to the teriparatide WAC (resulting in a price of $1,866 per pen), based on data provided by SSR Health combining data on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payers.[30] Net pricing data for abaloparatide was unavailable due to the agent's recent approval, so we assumed a discount of 27% from WAC (resulting in a price of $1,186 per pen), representing the average industry-wide discount for branded drugs.[31] Other non-drug costs such as fracture treatment costs and administration costs for zoledronic acid were derived from the published literature. All costs were converted to 2016 US dollars.

Model outputs include total costs, quality-adjusted life years (QALYs), life years for the interventions and comparators, and incremental costs per additional QALY and life year gained for the two interventions versus zoledronic acid. In addition to a base case analysis, sensitivity analyses using ranges of values for model inputs were conducted. Further details of the model structure and assumptions are provided in Chapter 6 of the full report.

Base-Case Results

The anabolic therapies resulted in increased costs, QALYs, and life years compared to zoledronic acid (Table ES6). QALYs gained versus zoledronic acid ranged from 0.066 for abaloparatide to 0.046 for teriparatide over the lifetime horizon. Incremental costs versus zoledronic acid ranged from a low of $22,061 for abaloparatide to $43,440 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 ES7).

Table ES6. Base-Case Results

Regimen	Cost	QALYs	Life Years
Zoledronic acid	$25,465	8.933	12.188
Teriparatide	$68,905	8.979	12.193
Abaloparatide	$47,525	8.999	12.195

QALY: quality-adjusted life year

Table ES7. Pairwise Results for Anabolic Therapies Compared to Zoledronic Acid

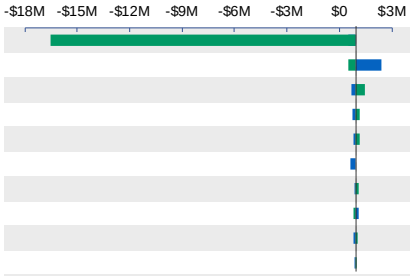
Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Teriparatide	$43,440	0.046	0.005	$941,537
Abaloparatide	$22,061	0.066	0.007	$333,892

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

Sensitivity Analysis Results

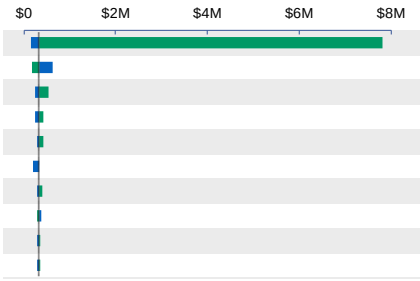
Detailed findings from the one-way sensitivity analyses varying the model inputs for anabolic agents versus zoledronic acid can be found in Figures ES1 and ES2. Parameters associated with hip fractures were the largest contributors to uncertainty for abaloparatide and teriparatide versus zoledronic acid, 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 vs. untreated patients). Results were also sensitive to uncertainty in the long-term utility multipliers and drug costs. None of the modeled parameters' range values resulted in ICERs less than $150,000 per QALY gained. (Negative ICERs shown below result from negative incremental QALYs vs. zoledronic acid.)

Figure ES1. Incremental Cost-Effectiveness Results of One-Way Sensitivity Analyses for Teriparatide Versus Zoledronic Acid



Parameter	Low Value	High Value	Low Result	High Result	Spread
Teriparatide Relative Risk: Hip Fracture	0.280	0.750	$479,590	-$16,532,705	$17,012,296
Zoledronic Acid Relative Risk: Hip Fracture	0.420	0.830	$2,384,332	$482,093	$1,902,239
Utility Multiplier: Hip Fracture Year 2+	0.640	0.960	$700,502	$1,435,465	$734,963
Cost: Teriparatide 600 mcg/2.4mL pen	$1,493	$2,240	$737,109	$1,145,966	$408,857
Teriparatide Relative Risk: Vertebral Fracture	0.090	0.290	$833,277	$1,165,710	$332,433
Utility Multiplier: Other Fracture Year 2+	0.800	1.000	$637,548	$941,537	$303,990
Teriparatide Relative Risk: Other Fracture	0.410	0.880	$840,319	$1,110,995	$270,675
General Population Utility: Age 80+	0.576	0.864	$1,081,405	$833,707	$247,698
Utility Multiplier: Vertebral Fracture Year 2+	0.745	1.000	$781,722	$1,018,714	$236,992
Utility Multiplier: Other Fracture Year 1	0.722	1.000	$838,241	$1,009,089	$170,848

Figure ES2. Incremental Cost-Effectiveness Results of One-Way Sensitivity Analyses for Abaloparatide Versus Zoledronic Acid



Parameter	Low Value	High Value	Low Result	High Result	Spread
Abaloparatide Relative Risk: Hip Fracture	0.171	0.741	$165,144	$7,807,367	$7,642,223
Zoledronic Acid Relative Risk: Hip Fracture	0.420	0.830	$624,585	$181,708	$442,877
Utility Multiplier: Hip Fracture Year 2+	0.640	0.960	$243,159	$532,644	$289,485
Cost/pen: Abaloparatide	$949	$1,424	$250,425	$417,358	$166,933
Abaloparatide Relative Risk: Vertebral Fracture	0.030	0.330	$298,026	$435,752	$137,726
Utility Multiplier: Other Fracture Year 2+	0.800	1.000	$197,820	$333,892	$136,072
Abaloparatide Relative Risk: Other Fracture	0.280	0.850	$293,843	$405,122	$111,279
General Population Utility: Age 80+	0.576	0.864	$381,325	$296,954	$84,371
Utility Multiplier: Other Fracture Year 1	0.722	1.000	$289,681	$364,076	$74,395
Utility Multiplier: Vertebral Fracture Year 2+	0.745	1.000	$284,412	$356,900	$72,488

Probabilistic sensitivity analysis indicated that our ICER results are highly uncertain, but the probability that the ICERs for the anabolic therapies were below $150,000 per QALY gained were either low (abaloparatide: 7.1%) or zero (teriparatide). This was primarily due to the small QALY gains and higher prices of anabolics versus zoledronic acid.

In a scenario analysis of patient populations with a higher risk of fracture than in the base-case, fracture risks would need to be approximately 118% 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. Teriparatide did not approach commonly-cited cost-effectiveness thresholds until a >1000% increased risk of fracture was applied. We also considered a scenario in which patients may not be able to take zoledronic acid. 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. Increasing refracture risks resulted in modest improvements in incremental QALYs and cost; however, none of these improvements were sufficient to make the incremental cost-effectiveness ratios for anabolic agents fall below $150,000 per QALY.

Threshold Analysis Results

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 ES8, along with net price per pen (i.e., base-case cost).

Table ES8. Resulting Pen Prices for Each Anabolic Therapy to Reach Cost per QALY Thresholds

Drug	Base-Case Cost	$50,000/QALY	$100,000/QALY	$150,000/QALY
Teriparatide (cost per pen)	$1,866.34	$238.47	$329.77	$421.07
Abaloparatide (cost per pen)	$1,186.25	$379.30	$521.42	$663.55

QALY: quality-adjusted life year

Value-based Benchmark Prices

Our value-based benchmark prices for abaloparatide and teriparatide are presented in Table ES10. As noted in the initial ICER methods document (http://icer-review.org/wpcontent/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINALcorrected-8-22-1.pdf), the value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained.

For both abaloparatide and teriparatide, the discounts required to meet both threshold prices are greater than the current discounts from WAC (assumed 27% for abaloparatide, 38% for teriparatide).

Table ES10. Value-based Benchmark Prices for Abaloparatide and Teriparatide for Osteoporosis Treatment

Drug Name	Annual WAC per Pen	Net Price* per Pen	Cost to Achieve $100,000/QALY	Cost to Achieve $150,000/QALY	Discount from WAC to reach $100,000 and $150,000/QALY Threshold	Average Net Price Within Benchmark Range?
Teriparatide	$2,997.90	$1,866.34‡	$329.77	$421.07	86% to 89%	No
Abaloparatide	$1,625.00	$1,186.25†	$521.42	$663.55	59% to 68%	No

QALY: quality-adjusted life year, WAC: wholesale acquisition cost, WTP: willingness to pay

*Net price is the estimated price after discounts and rebates from WAC.

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

‡ Price per pen including 38% discount

Potential Budget Impact

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact of abaloparatide, calculating incremental health care costs (including drug costs) minus any offsets in these costs from averted health care events. We did not estimate the budget impact of teriparatide, given its established presence in the market.

The potential budget impact was defined as the total incremental net cost of using abaloparatide, taking market share from teriparatide and zoledronic acid in the ratio 80:20 over a five-year time horizon. 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, 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.[32] Of those receiving treatment, 66% were diagnosed with osteoporosis while the remaining were treated for osteopenia.[32] 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.[32] This high-risk population was assumed to be eligible to receive treatment with abaloparatide. Applying these estimates to the projected 2017 US population resulted in an estimate of approximately 2.47 million eligible patients in the US.

Table ES9 below illustrates the per-patient budget impact results in more detail. Costs for abaloparatide were calculated using the WAC, discounted WAC, and three threshold prices. The discounted WAC price of teriparatide was derived from the SSR database, and average WAC price for generic zoledronic acid was 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 WAC, discounted WAC and across all three cost-effectiveness thresholds, ranging from approximately -$120 per patient using the WAC price ($1,625), to approximately -$10,500 per patient using the price to achieve $50,000 per QALY ($379).

Table ES9. 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	$13,952	$10,290	$5,928	$4,742	$3,556
Teriparatide + Zoledronic acid* (Discounted WAC Only)	$14,072				
Difference	-$120†	-$3,782†	-$8,144†	-$9,330†	-$10,516†

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

†Indicates cost-saving

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

Summary and Comment

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 a 38% and 27% discount on list prices of teriparatide and abaloparatide, respectively. This finding remained robust 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 are delayed, 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, 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 incremental 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 were the most severe fractures in the hierarchy. We attempted to mitigate the influence of hip fracture 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, our base-case cost and cost-effectiveness results for anabolics reflect our current assumptions about drug price. 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 analysis for abaloparatide indicates that use in place of teriparatide and zoledronic acid is not likely to generate access or affordability alerts when using WAC, discounted WAC, or the prices to achieve cost-effectiveness thresholds of $150,000 per QALY or lower.

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.[33] 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). All three anabolic drugs are delivered via subcutaneous injection. This assessment will focus on abaloparatide and teriparatide, because the FDA is no longer expected to issue a decision on romosozumab in 2017.[4].

Scope of the Assessment

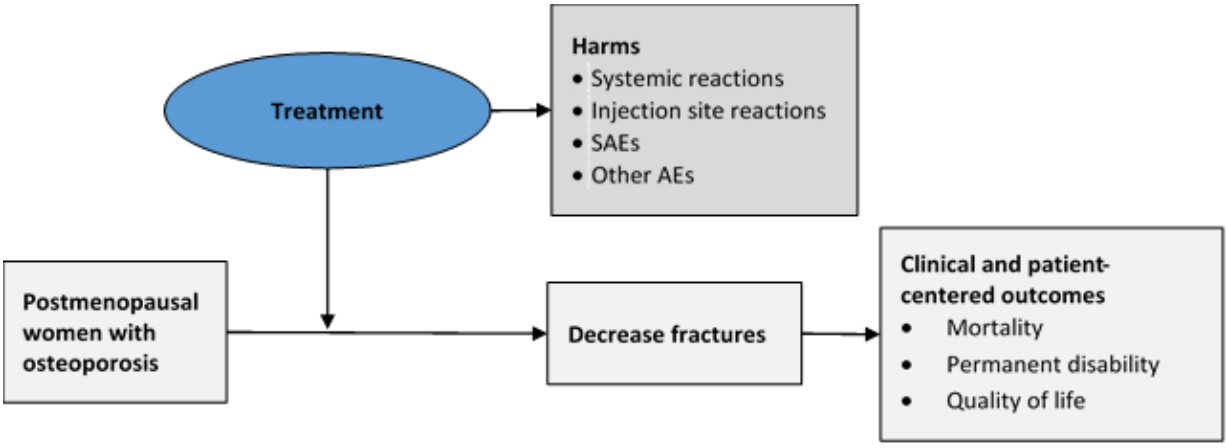
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was abstracted from randomized controlled trials.

There was only one head-to-head study of these interventions with fracture outcomes,[18] 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 is 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.)

Due to the delay in FDA consideration of romosozumab announced after the release of our draft report, we have limited the evaluation of the drug to the presentation of clinical trial results. We have not included romosozumab in the network meta-analysis or in the cost-effectiveness model, nor have we made any judgements regarding the comparative effectiveness of romosozumab to the other agents.

Comparators

We compared abaloparatide and teriparatide 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.

Clinical Outcomes	Key harms
Hip fractures	Atypical femoral fractures
All fragility fractures	Osteonecrosis of the jaw
Clinical vertebral fractures	Osteosarcoma
Living independently	Significant adverse events
Mobility	Adverse events leading to discontinuation
Pain	Injection site reactions
Ability to attend to activities of daily living	Hypocalcemia/Hypercalcemia
Quality of life	

Non-clinical Outcomes
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, including community dwelling and institutionalized populations.

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.[34]

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 approximately half of white 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 fracture from a low-energy injury 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.[35] However, screening rates are only about 26% for women 65 to 74 years of age.[36] The assessment of bone mineral density or treatment for osteoporosis is also a Health Effectiveness Data and Information Set (HEDIS) quality measure for older women.[37]

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), the North American Menopause Society (NAMS), and the American College of Physicians (ACP).[5-9] 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 may also be 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, less evidence of efficacy, route of administration, and/or cost.

Osteoporotic fractures can lead to pain, disability, and death. Even vertebral fractures that do not come to clinical attention may result in loss of height and pronounced curving of the spine (kyphosis) that interferes 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.[10] 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.[6]

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 estimate that only 45% of patients remain adherent with oral bisphosphonate therapy one year after the initial prescription and only 30% after two years.[11] 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.[12] 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.[12]

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) and PTH-related Protein (PTHrP) 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.[13] Teriparatide requires a daily injection of 20 mcg under the skin and the drug must be kept refrigerated. Patients are supplied with a pen injector that contains 28 daily doses, which translates to approximately 13 pens per year. 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 PTHrP analog, approved by the FDA on 4/28/17.[14] 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.[15] Abaloparatide requires a daily injection of 80 mcg under the skin, but does not require refrigeration after the first dose from each 30-day supply of injector pens. Abaloparatide is administered by a pen injector containing 30 daily doses, or approximately 12 pens per year.

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, and a decision in 2017 is no longer anticipated while the FDA reviews data from the ARCH trial that includes an unexpected safety signal regarding serious cardiovascular adverse events.[4]

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 do not come to clinical attention. 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**.

Morphometric vertebral fractures are typically assessed in two ways: semiquantitative (SQ) and quantitative morphometry (QM). The SQ assessment is typically performed by a radiologist who grades each vertebra on lateral radiographs of the spine according to a standard scale (Table 2). For QM assessment, six points are placed on a digital image of the vertebral body at the four corners and the midpoints of the endplates. The height of the vertebral body is measured in three places: anterior, middle, and posterior. Three ratios are typically calculated (anterior height/posterior height; middle height/posterior height, and posterior height/posterior height of adjacent vertebrae. A fracture is typically diagnosed when any of the three ratios are more than three standard deviations or greater from the mean of a reference population for that vertebra (prevalent fractures) or a decrease of at least 20% in height compared to prior imaging of the same vertebra (incident fractures). Each of the approaches has some subjectivity, so they are often combined with one approach used to confirm the other or requiring agreement from more than one radiologist. The optimal definition remains controversial.

Table 2. Grading of Vertebral Fractures

Decrease in Height	Category
< 20%	Normal (Grade 0)
20% to 25%	Mild (Grade 1)
26% to 40%	Moderate (Grade 2)
>40%	Severe (Grade 3)

The subset of morphometric fractures that come to clinical attention are called **clinical vertebral fractures**.

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

Non-vertebral fractures: Non-vertebral fractures exclude fractures of the skull, face, fingers, toes, metacarpals, and vertebrae as well as pathologic fractures and fractures associated with severe trauma.

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.[16] 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 with all of the anabolic therapies.

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). We focused on policies pertaining to teriparatide, abaloparatide, 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, teriparatide, or abaloparatide. California DHCS listed both alendronate and zoledronic acid, but not teriparatide and abaloparatide, on its contract drug list.[38]

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).[39-45] 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.[46-49] Two payers, Cigna and UHC, covered teriparatide with no additional requirements for patients with T-scores of -3.5 or lower.[50] Humana did not require a T-score, only that patients demonstrate the failure of or contraindication/intolerance to one oral bisphosphonate.[51] 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.

As of June 14, 2017, only one payer (Humana) had updated their publicly available Part D Formulary to mention abaloparatide; the payer does not cover the drug under its Part D Plans.[44]

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.[52-54] 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).[43,55-58] 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.[59] As of June 14, 2017, only two payers listed abaloparatide in their exchange formularies; Anthem listed the drug as non-formulary (i.e., coverage would require an exception), and Health Net listed the drug at the specialty tier. 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 BP	1 oral BP/SERM	1 oral BP and denosumab	1 oral BP	1 BP	None	1 monthly BP and denosumab
I/C	2 oral BP	2 oral BP or SERMs	1 oral BP and denosumab	2 oral BPs	1 BP	None	1 monthly BP 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 BP	None	None	1 oral BP§
I/C	None	None	None	1 oral BP	None	None	1 oral BP§

BP: 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[6]

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 recommend 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 College of Physicians (ACP), 2017[9]

The ACP guidelines, which are based on a systematic review conducted for the Agency for Healthcare Research and Quality (AHRQ), recommend pharmacologic treatment for women with osteoporosis, defined as a T-score of ≤ -2.5 or a history of fragility fractures. Alendronate, risedronate, zoledronic acid, and denosumab are recommended as first-line treatment options, while the use of both raloxifene and estrogen therapy with or without a progestogen is discouraged. The ACP recommends that pharmacologic treatment continue for up to five years, but noted that there is low-quality evidence to suggest an optimal treatment duration. BMD monitoring during pharmacologic treatment is not recommended; the ACP notes that there is no current evidence demonstrating that such monitoring provides any benefit. Decisions to treat women with osteopenia who are over the age of 65 should be made based on individual patient preference, fracture risk, the balance of benefits and harms, and cost considerations.

American Society for Bone and Mineral Research (ASBMR), 2016[5]

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[7]

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[8]

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[60]

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 discussions, 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 teriparatide, abaloparatide, and zoledronic acid. 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.[6] Similarly, the FDA indication for teriparatide and abaloparatide are identical, with both drugs being "indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy."[13,15] 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 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.[61,62] The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[63] 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.

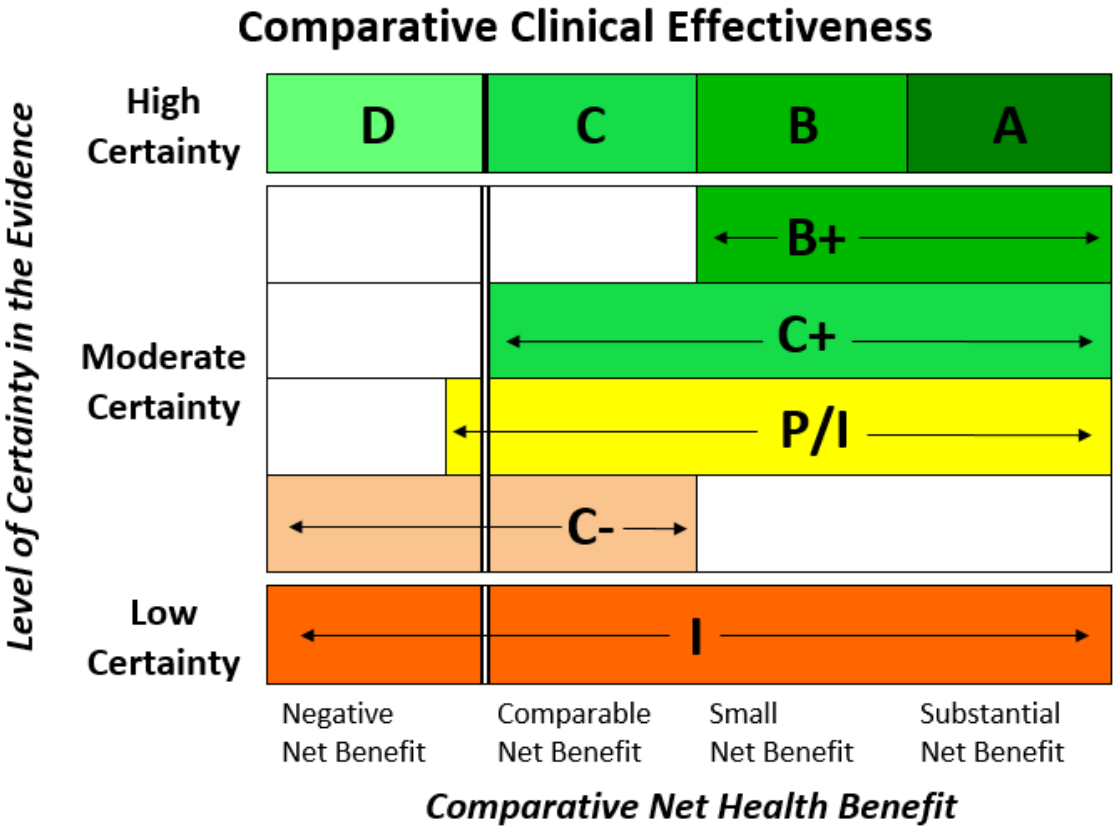
Information from the accepted studies was extracted into data extraction forms and summarized in Appendix Tables E1-E7.

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.[64]

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.[65] 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 10,000 iterations each were used for both "burn-in" (for model convergence) and model (for model results) simulations. The fixed effects model was chosen as the primary analysis because it is standard practice within a Bayesian environment when the network is almost entirely made up of single study connections. We report the results from random effects models with vague priors in Appendix Tables E10-11: the credible intervals from the random effects NMA are many orders of magnitude wider than those of the original trial results, which reflects the poor accuracy of random effects models when there are primarily single study connections in the network. We performed NMAs for morphometric vertebral fractures and non-vertebral fractures. There was insufficient data to evaluate hip fractures in an NMA. As noted above, we excluded romosozumab from all comparative effectiveness analyses including the NMAs.

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. Multiple stakeholders recommended using zoledronic acid as the comparator because it is a parenteral therapy like the anabolic agents and is used for the same indications (women at very high risk for fracture and those unable to tolerate oral therapy).

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.[17-19] Details of the studies are summarized in Appendix Tables E1-E7 and briefly in Table 4.

Table 4. Summary of the Randomized Trials of Anabolic Agents and Zoledronic Acid for Osteoporosis

Reference	Study	Group	N	F/U, months	Age, years	BMI, kg/m^2	Prior Fracture
Neer 2001[19]	Fracture Prevention Trial	Teriparatide Placebo	541 544	21 21	69 69	26.8 26.7	100% V
Miller 2016[18]	ACTIVE	Abaloparatide Teriparatide Placebo	824 818 821	18 18	69 69	25.0 25.2 25.1	24% V 63% any
Cosman 2016[17]	FRAME	Romosozumab Placebo	3589 3591	12 12	71 71	24.7 24.7	18% V 22% non-V
Black 2007[20]	HORIZON	Zoledronic acid Placebo	3889 3876	36 36	73 73	25.1 25.4	63% V

BMI: body mass index, F/U: follow-up, Non-V: non-vertebral fracture, V: vertebral fracture

Key Studies

The Fracture Prevention Trial – Teriparatide[19]

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.[19] 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 assessed using the semiquantitative (SQ) approach by a single reading by a radiologist at a central location who was blinded to treatment allocation, but not the order of the radiographs. 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.

Eight years later, the investigators re-analyzed the vertebral fracture data using quantitative morphometry (QM).[21] An incident vertebral fracture had to meet the following 3 criteria: 1) 20% decrease in height by quantitative morphometry, 2) a 4 mm decrease in height, and 3) an increase of at least one grade by visual SQ morphometry. Using this definition 1.8% of patients in the teriparatide group and 11.4% of the placebo group had incident vertebral fractures (RR 0.16, 95% CI 0.08-0.33). Note that this incidence of new vertebral fractures using this definition is markedly lower than that reported in the original publication (1.8% vs. 5% in teriparatide group and 11.4% vs. 14.3% in the placebo group). We have decided to use these estimates in our base-case analyses of vertebral fractures because the other pivotal trials used a two-step approach for diagnosing incident vertebral fractures.

The ACTIVE Trial – Abaloparatide[18]

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.[18] 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 defined using the SQ method with each fracture confirmed by a second radiologist also using the SQ technique. 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 non-vertebral 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.[66] 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[17]

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.[17] 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. Incident vertebral fractures were defined as an increase of at least one severity grade using the SQ method. Confirmation by a second radiologist was not reported in the primary publication or the study protocol, so this outcome may be similar to that reported in the original Fracture Prevention Trial publication.[19] 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[20]

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.[20] 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. Incident vertebral fractures were defined by a reduction in vertebral height of at least 20% and 4 mm by QM confirmed by an increase of one or more severity grades using the SQ method. 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.[20]

Morphometric Vertebral Fractures

The pivotal trials of teriparatide, abaloparatide, and zoledronic acid all reported a significant reduction in vertebral fractures versus placebo (Appendix Table E6), though the definition of incident vertebral fractures differed somewhat between trials. We elected to use a secondary analysis of incident vertebral fractures for the Fracture Prevention Trial[21] for primary inputs to this NMA because the definition was closer to that used in the ACTIVE trial.[18] The results of the NMA (Table 5) confirmed that all three drugs were significantly better than placebo at reducing morphometric vertebral fractures. Neither of the two anabolic agents was significantly different from the other, nor were they significantly different from zoledronic acid: the credible intervals for each of the comparisons between active drugs each contain 1 (Table 5). We performed multiple sensitivity analyses including 1) using the original definition of vertebral fractures in the Fracture Prevention Trial, 2) excluding the open-label teriparatide data from the ACTIVE trial, and 3) using a random-effects model (Appendix Table E10), but the primary conclusions did not change.

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

Abaloparatide (80 mcg)			
0.76 (0.20 – 2.26)	**Teriparatide (20 mcg)**		
0.44 (0.12 – 1.15)	0.57 (0.30 – 1.02)	**Zoledronic Acid (5 mg)**	
0.13 (0.03 – 0.33)	**0.17 (0.09 – 0.29)**	**0.30 (0.24 – 0.37)**	**Placebo**

*Includes data from open-label teriparatide arm of the ACTIVE trial[18] and from the secondary analysis of vertebral fractures for the Fracture Prevention Trial.[21]
Fixed-effects model; resdev = 5.646, DIC = 47.781
Legend: Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.

As expected, the NMA estimates for the reduction in vertebral fractures for each drug versus placebo are similar to the direct estimates versus placebo in the randomized trials (Table 6).

Table 6. Comparison of the Relative Risk Versus Placebo for Morphometric Vertebral Fractures between the Network Meta-Analysis and the Randomized Controlled Trials

Drug	NMA Estimate	RCT Estimates
Abaloparatide	0.13 (0.03-0.33)	0.14 (0.05-0.39)
Teriparatide	0.17 (0.09-0.29)	0.16 (0.08-0.33) 0.20 (0.08-0.47)
Zoledronic acid	0.30 (0.24-0.37)	0.30 (0.24-0.38)

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 7). Again, neither of the anabolic agents were significantly different from one another, nor were they significantly different from zoledronic acid. Zoledronic acid significantly reduced non-vertebral fractures in the HORIZON trial and in the NMA. Again, we performed sensitivity analyses including 1) excluding the open-label teriparatide data from the ACTIVE trial, and 2) using a random-effects model (Appendix Table E11).

Table 7. Network Meta-Analysis Results for the Relative Risk of Non-Vertebral Fragility Fractures*

Abaloparatide (80 mcg)			
0.83 (0.46 – 1.46)	**Teriparatide (20 mcg)**		
0.69 (0.38 – 1.16)	0.82 (0.54 – 1.22)	**Zoledronic Acid (5 mg)**	
0.51 (0.28 – 0.85)	**0.61 (0.41 – 0.88)**	**0.75 (0.64 – 0.87)**	**Placebo**

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

Fixed-effects model; resdev = 6.518, DIC = 52.897

Legend: Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.

As with vertebral fractures, the NMA estimates for the reduction in non-vertebral fractures for each drug versus placebo are similar to the direct estimates versus placebo in the randomized trials (Table 8).

Table 8. Comparison of the Relative Risk versus Placebo for Non-Vertebral Fractures between the Network Meta-Analysis and the Randomized Controlled Trials

Drug	NMA estimate	RCT estimates
Abaloparatide	0.51 (0.28-0.85)	0.57 (0.32-1.00)
Teriparatide	0.61 (0.41-0.88)	0.47 (0.25-0.88) 0.72 (0.42-1.22)
Zoledronic acid	0.75 (0.64-0.87)	0.75 (0.64-0.87)

Hip Fractures

Among the anabolic studies the incidence of hip fractures was low (7 hip fractures total in the abaloparatide and teriparatide studies). Only the FRAME study reported relative risks (Appendix Table E6). Hip fractures were significantly reduced for zoledronic acid compared to placebo in the HORIZON trial (RR=0.59, CI 0.42-0.83). Relative risk estimates for abaloparatide and teriparatide were not reported in the clinical trials. We examined a network meta-analysis, but the results were unstable and 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 lack of face validity of these estimates, we did not use them in assessing the comparative effectiveness of these drugs, nor were the estimates used in our cost modeling.

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 9 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. Half of patients treated with abaloparatide developed anti-abaloparatide antibodies, but these did not significantly impact fracture efficacy or adverse events.

Table 9. 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[19]	Teriparatide Placebo	NR NR	6% 6%	NR NR	NR NR	No sign. diff.	11% 2%
Abaloparatide							
Miller 2016[18]	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[17]	Romosozumab Placebo	9.6% 8.7%	2.9% 2.6%	1 0	1 0	NR NR	NR NR
Key comparator: Zoledronic acid							
Black 2007[20]	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 risk for atypical femoral fractures and osteonecrosis of the jaw with bisphosphonates. However, the risk is low. It is estimated that treatment of 10,000 women with zoledronic acid for three years would prevent approximately 710 vertebral fractures, 110 hip fractures, while causing one atypical femoral fracture and less than one case of osteonecrosis of the jaw.[67] 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.[12]

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. Similarly, we used the original Fracture Prevention Trial definition of vertebral fracture in a sensitivity analysis. Finally, we performed random effects models in addition to the primary fixed effects models. 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 a slight increase in the reduction of non-vertebral fractures). Results from NMA sensitivity analyses are reported in Appendix Tables E8-E11

Observational Study Results for the Anabolic Agents

There are no observational data available for abaloparatide or romosozumab that met our search criteria. Teriparatide, on the other hand, has been in clinical use for more than a decade. No studies reported on morphometric fractures, because these require baseline and follow-up lateral spine x-rays without symptoms. The observational data report a 40% to 73% reduction in clinical vertebral fractures.[22,68,69] The observed reduction in non-vertebral fractures ranged from 38% to 45%.[22,68,70] Importantly, there was also a significant 45% reduction in hip fractures in one claims database (odds ratio [OR] 0.55, 95% CI 0.42-0.74).[22] This is particularly important as the randomized studies of teriparatide had insufficient power to demonstrate a reduction in hip fractures.

Unpublished Trials

The VERO Study (Teriparatide vs. Risedronate)

The Vertebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) trial was presented at the World Congress on Osteoporosis, Osteoarthritis and Muscular Disease in March 2017.[71] The investigators randomized 1360 women with at least two moderate or one severe vertebral fracture and a T-score ≤ -1.5 to two years of teriparatide 20 mcg SC daily or the oral bisphosphonate risedronate 35 mg once a week. Compared with risedronate, patients treated with teriparatide had significantly fewer new vertebral fractures (5.4% vs. 12.0%, HR 0.44, p<0.001) and a non-significant reduction in non-vertebral fragility fractures (4.0% vs. 6.1%, HR 0.66, p=0.099). Adverse events that were more common in the teriparatide group included extremity pain (5.4% vs. 2.6%, p = 0.013), dizziness (4.4% vs. 1.8%, p=0.007, hypercalcemia (2.2% vs. 0.1%, p<0.001), and decreased vitamin D (1.3% vs. 0.1%, p=0.021).

These results support the hypothesis that teriparatide prevents more vertebral fractures than risedronate over two years of therapy. The study did not have sufficient power to demonstrate a reduction in non-vertebral fractures or hip fractures.

The ARCH Study (Romosozumab Followed by Alendronate vs. Alendronate Alone)

The double-blind, placebo-controlled ARCH study results were announced in a press release by Amgen on May 21, 2017.[4] The investigators randomized 4,093 postmenopausal women to either romosozumab 210 mg SC every month for 12 months followed by the oral bisphosphonate alendronate for 12 months or alendronate 70 mg orally once weekly for 24 months. The sequence of romosozumab followed by alendronate significantly reduced the incidence of new vertebral fractures (HR 0.50) and clinical fractures (HR 0.73) compared to alendronate alone. The sequenced therapy also significantly reduced the incidence of non-vertebral fractures (HR 0.81). However, there was a concerning safety signal. The incidence of new serious cardiovascular events was

higher in the romosozumab group at one year (2.5% vs. 1.9%). There were also more injection site reactions in the romosozumab group (4.4% vs. 2.6%)

These results support the hypothesis that starting therapy with an anabolic agent and sustaining the gains with an anti-resorptive agent may be more effective at preventing vertebral and non-vertebral fractures than treating with an anti-resorptive agent for two years. The increase in serious cardiovascular events was not observed in the larger FRAME study (n=7,180), so the observed increase in the ARCH study may be a chance finding. The ARCH study has not yet been presented at a conference or published in a peer reviewed journal, which limits our ability to fully evaluate these results.

Controversies and Uncertainties

The primary controversy is whether it was appropriate to combine the data from the different study populations of the three trials in a NMA. There were 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 (Table 4). In order for the NMA results to be invalid, there must be effect modification in the relative rate of fractures for one or more of the drugs by patient characteristics that differ significantly between trials. 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[72], abaloparatide[73], and romosozumab.[17] In all three analyses, risk factors for fracture did not modify the relative 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 10).

Table 10. 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	6.5	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.

None of the published NMAs of drug therapy for osteoporosis included abaloparatide (see Appendix C).[23-27] Similar to our findings, the NMAs concluded that both teriparatide and zoledronic acid reduce the risk of vertebral and non-vertebral fractures compared to placebo. They found no significant differences between the drugs, though teriparatide ranked higher than zoledronic acid. They also concluded that zoledronic acid reduced hip fractures, but there was insufficient evidence for teriparatide.

A major area of uncertainty is due to 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, 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. Indeed, the recent ACP clinical guideline did not recommend any of the anabolic agents as first-line therapy for osteoporosis because of the lack of randomized trial evidence on hip fracture prevention.[9]

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. However, in the HORIZON trial, the reductions seen with zoledronic acid 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. Indeed, the disconnect between change in bone mineral density and reduction in fractures has been widely recognized for bisphosphonates.[74-76] 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.[28] 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 previously treated with anti-resorptive drugs.[29] This suggests that anabolic agents may be most effective if used prior to anti-resorptive therapy. 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 two anabolic agents reduce vertebral fractures compared to no therapy. 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 both initial anabolic therapy and subsequent anti-resorptive therapy is essential to preserve the fracture reduction benefit. However, there are minimal real-world data available to compare adherence to therapy between the two anabolic agents.

For the two anabolic agents, we judged 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 non-vertebral fractures, and uncertain benefits for hip fractures, though observational data do support a benefit for teriparatide.

When abaloparatide is compared to teriparatide, we judged that the evidence is insufficient to assess the comparative clinical effectiveness of the two drugs. The extensive real world clinical experience with teriparatide without identification of new adverse events and observational evidence confirming benefits is reassuring. However, in the ACTIVE trial, there was a non-significant trend towards greater reduction in both vertebral and non-vertebral fractures with abaloparatide compared with teriparatide.

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. 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 a similar mechanism as teriparatide. However, both anabolic drugs work through a fundamentally different mechanism from the other available agents, including zoledronic acid. There is evidence that starting with an anabolic agent followed by an antiresorptive agent may result in greater long-term fracture prevention than treating with an antiresorptive agent for the same length of time. However, to date, there are no published randomized trials demonstrating that this is the optimal approach.

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. Economic Analyses

6.1 Long-Term Cost-Effectiveness

Overview

We conducted a cost-effectiveness analysis using a simulation model comparing the two FDA-approved anabolic therapies, abaloparatide and teriparatide, to 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, 3) patients at higher risk of fracture are recommended to receive this drug, and 4) clinical experts indicated it was the most appropriate comparator. We estimated the costs, numbers of fractures, quality-adjusted life years (QALY) gained, life-years gained and the incremental cost-effectiveness of the anabolic agents 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, hip, and all other non-vertebral fractures
- Life expectancy
- Quality-adjusted life-years (QALYs)
- Osteoporosis drug treatment costs
- Fracture costs
- Total costs
- Costs per QALY gained

Cost-Effectiveness Model: Methods

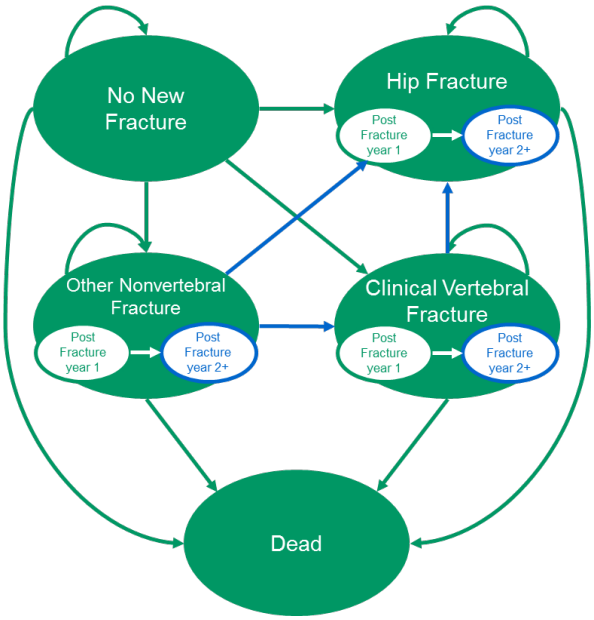
Model Structure

The primary aim of this analysis was to estimate the cost-effectiveness of treatments indicated for the prevention of osteoporotic fractures in postmenopausal women who have not been recently treated for osteoporosis, but have an indication for treatment to prevent osteoporotic fractures. The model adopted a health care system perspective. This *de novo* model was built in Microsoft Excel and the model structure is depicted in Figure 3, and is based in part on a literature review of prior published models of osteoporosis.[77] A representative cohort of patients at high fracture risk who are untreated or have not recently received treatment were modeled from treatment initiation until death. Patients transitioned between health states during one-year cycles over a lifetime time

horizon. The model used a 3% discount rate for costs and health outcomes, and costs are presented in 2016 US dollars.

The model consists of several health states, including osteoporosis without a new fracture (the origination state for patients entering the model), clinical vertebral fracture, hip fracture, other (i.e., non-hip) non-vertebral fracture, and death; fracture health states reflect those examined in the network meta-analysis (NMA). Patients may also have a morphometric vertebral fracture but we assumed they do not change health states, due to the negligible cost and QALY impacts of morphological vertebral fractures; we explored a potential QALY loss for these patients in a scenario analysis. 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. Given this constraint, we calibrated the model so that the cumulative fracture probabilities for an untreated (baseline) population were representative of expected rates for each fracture type, as described below. The assumed hierarchy of fracture severity is hip > vertebral > other.

Figure 3. Markov Model Structure for Osteoporosis Patients



Target Population

The population of focus is postmenopausal women who are untreated or 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.[17-19]

Key Model Characteristics

The model utilizes results from the NMAs in the evidence review as well as imputed values for hip fracture (see Table 11 for a detailed explanation) as the effectiveness estimates for fracture prevention for each drug regimen (Table 12). We applied the relative risk estimates derived from the NMA and the imputed hip fracture relative risks to the baseline fracture probabilities, which were derived from a combination of clinical trials, the published literature, and the FRAX Fracture Risk Assessment Tool.[17-19,78-80] 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.[81] Patient mortality was based on US background age-related mortality estimates for females; hip fracture was assumed to increase the risk of mortality.

The model includes treatment costs associated with each individual regimen, including drug acquisition costs, administration 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.[82]

Key Model Assumptions

Table 11 contains a list of key model assumptions along with the rationale for each assumption.

Table 11. Key Model Assumptions

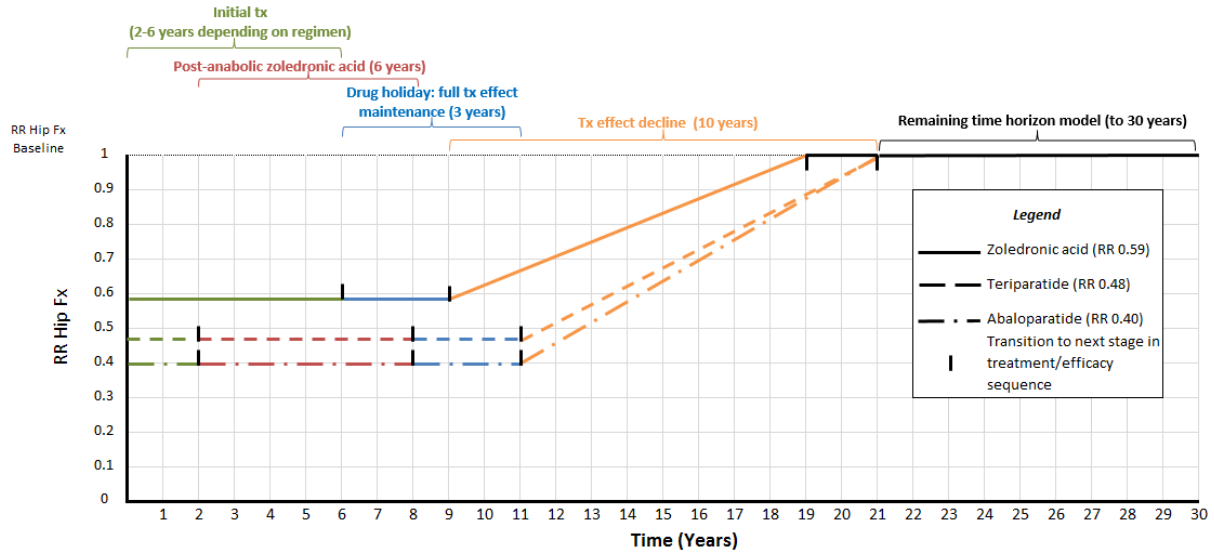
Assumption	Rationale
From a post-fracture state, patients can transition to a worse fracture state only (or death). The hierarchy for fracture severity is hip > vertebral > other.	Prevents patients who experience more serious fractures from forfeiting serious fracture states' associated long-term costs and utilities by transitioning to a less severe fracture in the "memory-less" Markov model framework.
Subject to the fracture hierarchy, patients may have an unlimited number of fractures over the modeled time horizon.	Real-world patients may experience any number of fractures.
Hip fracture relative risk estimates for anabolic drugs were based on the ratio of hip fracture relative risk vs. non-vertebral fracture relative risk reported in the HORIZON trial (zoledronic acid vs. placebo). Briefly, the HORIZON-derived ratio was 0.59 (hip) / 0.75 (non-vertebral) = 0.79, which was multiplied by the NMA-derived relative risks for non-vertebral fractures (abaloparatide = 0.51, teriparatide = 0.61) to obtain base case estimates. We then derived confidence intervals for sensitivity analyses based on the NMA-derived non-vertebral fracture ranges for each drug. We used the HORIZON trial's zoledronic acid relative risk (and confidence interval) for hip fracture directly.	Trial-observed hip fractures were rare for teriparatide and abaloparatide; thus, the NMA results for hip-only fractures were unstable and lacked face validity. Studies of osteoporosis drugs with adequate power to assess hip fractures consistently find that the reduction in hip fractures lies between that for vertebral fractures and non-vertebral fractures (see Appendix Table E6 for romosozumab and zoledronic acid).
We did not model serious adverse events in the base case analysis. We explored the impact of infusion reactions stemming from IV infusion of zoledronic acid in a scenario analysis based on the approach of a previous cost-effectiveness analysis of bisphosphonates.[23]	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.
Anabolic therapies are administered for a duration of two years according to their labeled indication, and are followed by six years of zoledronic acid. We assume that time to benefit for anabolic agents and zoledronic acid is immediate and that 100% anabolic efficacy is maintained throughout the anabolic and post-anabolic zoledronic acid periods, plus an additional 3 years, then efficacy declines linearly to a relative risk of 1 over a period of 10 years. **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.**	Anabolic treatment duration: FDA label Zoledronic acid treatment duration: AACE guidelines state that patients at high risk should be treated for six years. The HORIZON Extension Trials demonstrated added efficacy for six but not nine years of therapy and maintenance of efficacy for three years following treatment cessation.[83,84] 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.
All comparators' adherence rates were 100% in base case analysis.	Lack of real-world adherence data for abaloparatide, and on the impact of lower adherence on efficacy for abaloparatide and teriparatide.
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%.[31]

Treatment Strategies

The interventions assessed in the model were the same as those in the clinical evidence review (abaloparatide, teriparatide, and zoledronic acid). We compared 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. Patients received anabolic therapy for two years, immediately followed by six years of therapy with zoledronic acid. We assumed all therapies had 100% efficacy throughout the treatment regimen (i.e., no efficacy ramp-up time), and that the anabolic therapies' efficacy was maintained throughout the zoledronic acid administration period plus three years (i.e., 11 years total of 100% anabolic efficacy), before declining to a relative risk of 1.0 over a 10-year period. For zoledronic acid, we modeled a three-year efficacy maintenance period after the administration period ended (i.e., nine years total of 100% zoledronic acid efficacy), followed by an efficacy decline over 10 years. We also assumed 100% treatment adherence for all agents. Figure 4 represents an example of treatment sequencing and effect over time for hip fractures; the same approach was applied to clinical vertebral and to other non-vertebral 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 risks of fracture for each drug (Table 12) were derived from 1) the NMA (vertebral and non-vertebral fractures) and 2) the ratio of hip to non-vertebral fracture relative risks reported in the HORIZON trial (see Table 11 for additional hip fracture relative risk explanation); each relative risk estimate represents the differential risk of fracture versus placebo per year. Note that the NMA relative risk estimates for vertebral fracture include both clinical and morphometric vertebral fractures; because our modeled health states include only clinical vertebral fracture, while morphometric vertebral fracture patients are assumed to remain in their current health states, we assumed a 35% proportion of overall vertebral fractures were clinical vertebral fractures, reflecting the results of a retrospective cohort analysis.[78] In probabilistic sensitivity analyses (PSA), relative risk estimates were varied using a log-normal distribution; uncertainty in the proportion of vertebral fractures that were clinical was modeled as ±20% with a beta distribution.

Table 12. Fracture Relative Risk Parameters

Model Input	Default	Lower	Upper	Source
Zoledronic acid (baseline)				
Hip Fracture	0.59	0.42	0.83	Black et al., HORIZON trial[20]
Vertebral Fracture (all) *	0.30	0.24	0.37	NMA
Other Non-Vertebral Fractures	0.75	0.64	0.87	NMA
Teriparatide				
Hip Fracture	0.48	0.28	0.75	Derived from NMA and HORIZON
Vertebral Fracture (all)*	0.17	0.09	0.29	NMA
Other Non-Vertebral Fractures	0.61	0.41	0.88	NMA
Abaloparatide				
Hip Fracture	0.40	0.17	0.74	Derived from NMA and HORIZON
Vertebral Fracture (all)*	0.13	0.03	0.33	NMA
Other Non-Vertebral Fractures	0.51	0.28	0.85	NMA

*Relative risks for vertebral fractures were estimated from studies including morphometric vertebral fractures; 35% of estimated vertebral fractures were modeled as clinical vertebral fractures.

Baseline Fracture Inputs

The relative risk estimates from the NMA were applied to age-stratified baseline (placebo) estimates of annual probability of fracture to derive each comparator's annual fracture probabilities (Table 13). We derived the age-stratified baseline annual fracture probabilities by calculating the fracture risks of an average 70-year old patient from the pooled placebo arms of the Fracture Prevention, ACTIVE, FRAME, and HORIZON trials. Briefly, we summed 1) the number of each fracture type (hip, vertebral, and non-vertebral) from the trials, as well as 2) the fracture types' associated follow-up time in person-years, then calculated annualized rates of each fracture type. These annualized rates were then converted to annual probabilities that we used as the baseline fracture probabilities for patients age 70-74 years.

To model increasing fracture risk as patients age, we extrapolated pooled estimates based on 1) previously published age-stratified fracture estimates[78] and 2) the 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; note that FRAX was only utilized for the derivation of hip fracture estimates.[81]

We used data reported by 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 (9.5%). 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 13. Baseline (Placebo) Annual Fracture Probabilities by Age Strata

Fracture and Age (in years) 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[78]/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 (Clinical and Morphometric)				
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 Non-Vertebral 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 all but one study did not control for comorbidities. The study that did control for underlying health status found that excess mortality occurred after hip fractures (vertebral and non-vertebral fractures were not considered) at a rate roughly 50% lower than studies that adjusted for age and gender only.[85] 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 14). The excess mortality estimates were then added to

the background mortality estimates of the US population at each model cycle for hip fracture patients.[81] All excess mortality parameters were varied using a log-normal distribution in a PSA.

Table 14. Absolute Mortality Increase for Hip Fracture

Age Range	Default	Lower	Upper	Source
Age 70-74	0.0025	0.0020	0.0029	Tosteson[85]
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 15).[86-90] The baseline utility estimates for patients with no new fracture were from a study of the non-institutionalized US adult population for 7 health-related quality-of-life scores; we used the EuroQoL-5D (EQ-5D) age-stratified estimates for US women.[86] We applied utility multipliers to baseline estimates for each fracture health state; utility multipliers were also derived using the EQ-5D index. 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;[78] non-clinical vertebral fractures had no utility multiplier applied in the base case analysis, however we explored this assumption in a scenario analysis (see Appendix Figure F5). 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 15. Utility Values by Age Strata and Utility Multipliers

Model Input	Default	Lower	Upper	Source
General Population Utilities				
Age 70-79	0.770	0.616	0.924	Hanmer et al.[86]
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.[89]
Hip Fracture Year 2+	0.800	0.640	0.960	Peasgood et al.
Clinical Vertebral Fracture Year 1	0.590	0.472	0.708	Peasgood et al.
Clinical Vertebral Fracture Year 2+	0.931	0.745	1.000	Kanis/Oleksik et al.[87,88]
Other Non-Vertebral Fracture Year 1	0.902	0.722	1.000	Burstrom et al.[90]
Other Non-Vertebral 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.[91] For the price of a teriparatide pen, we obtained data from SSR Health that combined information on net US dollar sales through the first quarter of 2017 with information on unit sales to derive net pricing at the unit level across all payer types.[30] We estimated net prices by comparing the four-quarter rolling averages (i.e., second quarter of 2016 through first quarter of 2017) 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 June 2017[91] to arrive at an estimated net price per pen. The derived discount for teriparatide was 38%, which was then applied to the WAC for a 2.4 ml (250 mcg/ml) package that resulted in a net price of $1,866.34 per pen. This discount may not reflect the negotiated price for any one payer, but rather the average discount across all payers. Each teriparatide pen contains 28 doses, so patients use approximately 13 pens per year. For abaloparatide, we used the announced list price of $1,625 per pen (as of June 1, 2017) and applied a 27% discount, representing the average industry-wide discount on brand drugs.[31,92] Each abaloparatide pen contains 30 doses, so patients use approximately 12 pens per year. In addition, threshold analyses on these costs are provided in the results section of this chapter. All drug costs were varied by ±20% using a normal distribution in the PSA.

Table 16. Drug Cost Inputs

Drug Name, Labeled Dose, Administration Route	Strength (Pen Size)	WAC/Pen	Net Price*	Base-Case Tx Duration	Acquisition Cost Per Tx Course†
Teriparatide 20 mcg SC QD	250 mcg/ml (2.4 ml)	$2,997.90	$1,866.34‡	2 years	$48,691
Abaloparatide 80 mcg SC QD	3,120 mcg/1.56 ml	$1,625	$1,186.25§	2 years	$29,312
Zoledronic Acid 5 mg IV Q year	5 mg/100 ml	$306#	$306#	6 years	$1,837

IV: intravenous, SC: subcutaneous, QD: once daily, Q mo: once monthly, 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 38% discount

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

#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 17).[93,94] 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;[78] non-clinical vertebral fractures had no fracture-related costs applied. We modeled administration cost for zoledronic acid intravenous administration ($168)[95] but not for anabolic drugs as they are self-administered. 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 17. Acute and Long-Term Annual Fracture Costs

Model Input	Default	Lower	Upper	Source
Hip Fracture Cost	$44,395	$35,516	$53,274	Bonafede[93]
Post-Hip Fracture Annual Cost	$10,835	$8,668	$13,002	Parthan[94]
Clinical Vertebral Fracture Cost	$27,906	$22,325	$33,487	Bonafede
Post-Clinical Vertebral Fracture Annual Cost	$309	$247	$371	Parthan
Other Non-Vertebral Fracture Cost	$12,764	$10,211	$15,317	Bonafede
Post-Other Non-Vertebral Fracture Annual Cost	$0	$0	$0	Assumption

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. 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).
9. The inclusion of a disutility for zoledronic acid infusion-related reaction (adverse event).
10. The inclusion of a disutility for morphometric vertebral fractures
11. Baseline fracture risk in higher risk patient groups who cannot tolerate zoledronic acid.

Cost-Effectiveness Model: Results

Base-Case Results

The anabolic therapies resulted in increased costs, QALYs, and life years compared to zoledronic acid (Table 18). The QALYs gained versus zoledronic acid were 0.066 for abaloparatide and 0.046 for teriparatide over the lifetime horizon (Table 19). Incremental costs were $22,061 for abaloparatide and $43,440 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 19).

Table 18. Base-Case Results

Regimen	Cost	QALYs	Life Years
Zoledronic acid	$25,465	8.933	12.188
Teriparatide	$68,905	8.979	12.193
Abaloparatide	$47,525	8.999	12.195

QALY: quality-adjusted life year

Table 19. Pairwise Results for Anabolic Therapies Compared to Zoledronic Acid

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Teriparatide	$43,440	0.046	0.005	$941,537
Abaloparatide	$22,061	0.066	0.007	$333,892

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

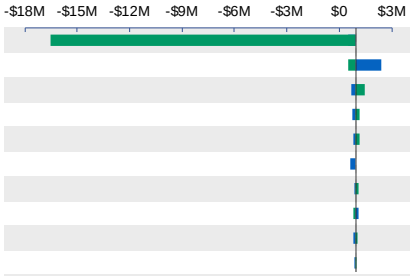
Appendix Tables F1-F2 provide additional detail regarding the model findings. First, there were moderate cost offsets compared to zoledronic acid due to fracture prevention, ranging from approximately -$5,300 for abaloparatide versus zoledronic acid to approximately -$3,500 for teriparatide versus zoledronic acid. These cost savings from prevention of fractures offset approximately 7-19% of the anabolic drug costs. The benefits to patients (measured in QALYs) resulted from small contributions across hip, clinical vertebral, and other non-vertebral 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 our ICER results are highly uncertain, but the probability that the ICERs for the anabolic therapies were below $150,000 per QALY gained

were either low (abaloparatide: 7.1%) or zero (teriparatide). 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 of model inputs for anabolic agents versus zoledronic acid can be found in Figures 5-6. Parameters associated with hip fractures were by far 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 vs. untreated patients). Results were also sensitive to uncertainty in the long-term utility multipliers and drug costs. None of the modeled parameters' range values resulted in an ICER less than $150,000 per QALY gained. (Negative ICERs shown below result from negative incremental QALYs vs. zoledronic acid.)

Figure 5. One-way Sensitivity Analysis: Incremental Cost-Effectiveness Ratios for Teriparatide Versus Zoledronic Acid



Parameter	Low Value	High Value	Low Result	High Result	Spread
Teriparatide Relative Risk: Hip Fracture	0.280	0.750	$479,590	-$16,532,705	$17,012,296
Zoledronic Acid Relative Risk: Hip Fracture	0.420	0.830	$2,384,332	$482,093	$1,902,239
Utility Multiplier: Hip Fracture Year 2+	0.640	0.960	$700,502	$1,435,465	$734,963
Cost: Teriparatide 600 mcg/2.4mL pen	$1,493	$2,240	$737,109	$1,145,966	$408,857
Teriparatide Relative Risk: Vertebral Fracture	0.090	0.290	$833,277	$1,165,710	$332,433
Utility Multiplier: Other Fracture Year 2+	0.800	1.000	$637,548	$941,537	$303,990
Teriparatide Relative Risk: Other Fracture	0.410	0.880	$840,319	$1,110,995	$270,675
General Population Utility: Age 80+	0.576	0.864	$1,081,405	$833,707	$247,698
Utility Multiplier: Vertebral Fracture Year 2+	0.745	1.000	$781,722	$1,018,714	$236,992
Utility Multiplier: Other Fracture Year 1	0.722	1.000	$838,241	$1,009,089	$170,848

Figure 6. One-way Sensitivity Analysis: Incremental Cost-Effectiveness Ratios for Abaloparatide Versus Zoledronic Acid

Parameter	Low Value	High Value	Low Result	High Result	Spread
Abaloparatide Relative Risk: Hip Fracture	0.171	0.741	$165,144	$7,807,367	$7,642,223
Zoledronic Acid Relative Risk: Hip Fracture	0.420	0.830	$624,585	$181,708	$442,877
Utility Multiplier: Hip Fracture Year 2+	0.640	0.960	$243,159	$532,644	$289,485
Cost/pen: Abaloparatide	$949	$1,424	$250,425	$417,358	$166,933
Abaloparatide Relative Risk: Vertebral Fracture	0.030	0.330	$298,026	$435,752	$137,726
Utility Multiplier: Other Fracture Year 2+	0.800	1.000	$197,820	$333,892	$136,072
Abaloparatide Relative Risk: Other Fracture	0.280	0.850	$293,843	$405,122	$111,279
General Population Utility: Age 80+	0.576	0.864	$381,325	$296,954	$84,371
Utility Multiplier: Other Fracture Year 1	0.722	1.000	$289,681	$364,076	$74,395
Utility Multiplier: Vertebral Fracture Year 2+	0.745	1.000	$284,412	$356,900	$72,488

Scenario Analyses

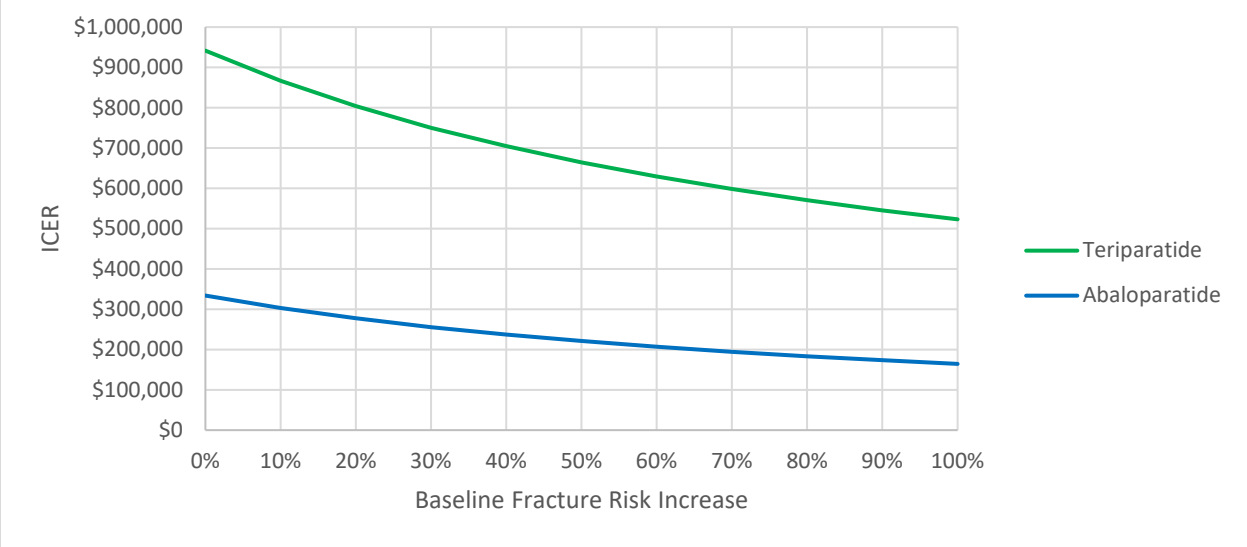
Below, we report the results of the most relevant or influential scenario analyses. Results from the scenario analyses pertaining to treatment efficacy ramp-up, maintenance, and rates of decline did not yield major differences in conclusions from the base case and can be found in Appendix Figures F1-F5 and Tables F3-F7. 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 three 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,[78] and the online FRAX tool[96] 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 7 below. Fracture risks must be approximately 118% 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. Teriparatide did not approach commonly-cited cost-effectiveness thresholds until a >1000% increased risk of fracture was applied.

Figure 7. 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 three years in the absence of zoledronic acid. The results for this scenario

are shown below in Tables 20 and 21. 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 three years up to 10 years (as in the base case analysis).

Table 20. Results of Scenario Analysis Comparing Anabolic Drugs to No Treatment

Regimen	Cost	QALYs	Life Years
No Treatment	$30,038	8.825	12.181
Teriparatide	$73,162	8.886	12.182
Abaloparatide	$52,919	8.893	12.183

QALY: quality-adjusted life year

Table 21. Pairwise Results of Anabolic Drugs Compared to No Treatment

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. No Treatment
Teriparatide	$43,124	0.060	0.002	$715,878
Abaloparatide	$22,881	0.067	0.002	$339,027

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

Increased Refracture Risk

In this scenario analysis, we further increased the refracture risk from baseline, using published estimates (Table 22)[97] to explore the impact on model results.

Table 22. Relative Risk of Subsequent Fracture for Scenario Analysis of Increased Refracture Risk

Model Input	Default	Source
Post-Hip Fracture RR: Hip Fracture	2.30	Klotzbuecher[97]
Post-Vertebral Fracture RR: Hip Fracture	2.30	Klotzbuecher
Post-Vertebral Fracture RR: Vertebral Fracture	4.40	Klotzbuecher
Post-Other Non-Vertebral Fracture RR: Hip Fracture	1.90	Klotzbuecher
Post-Other Non-Vertebral Fracture RR: Vertebral Fracture	1.70	Klotzbuecher
Post-Other Non-Vertebral Fracture RR: Other Fracture	3.30	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 24); however, none of these improvements were sufficient to make the incremental cost-effectiveness ratios for anabolic agents fall below $150,000 per QALY.

Table 23. Results When Including Increased Refracture Risk

Regimen	Cost	QALYs	Life Years
Zoledronic Acid	$32,129	8.864	12.170
Teriparatide	$74,109	8.927	12.179
Abaloparatide	$52,078	8.953	12.183

QALY: quality-adjusted life year

Table 24. 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
Teriparatide	$41,980	0.063	0.010	$662,149
Abaloparatide	$19,949	0.090	0.013	$222,548

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

Duration of Teriparatide and Abaloparatide Therapy as Studied in the Trials

In the Fracture Prevention Trial (teriparatide) and the ACTIVE trial (abaloparatide), patients were treated for 21 months and 18 months, respectively; however, their FDA labels both recommend treatment for up to two years, and we used the labeled indication in the base-case analysis. In this scenario analysis, we modeled the respective trial treatment durations, but assumed that efficacy was maintained for the entire two years. Zoledronic acid was administered for six years in both arms, as in the base case. This scenario showed lowered anabolic cost of both regimens, but did not impact QALYs because our assumptions regarding efficacy maintenance were unchanged from the base case.

Table 25. Results When Using Trial-Reported Time on Treatment for Anabolics

Regimen	Cost	QALYs	Life Years
Zoledronic Acid	$25,465	8.933	12.188
Teriparatide	$63,486	8.979	12.193
Abaloparatide	$41,020	8.999	12.195

QALY: quality-adjusted life year

Table 26. Pairwise Results When Using Trial-Reported Time on Treatment for Anabolics

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Teriparatide	$38,021	0.046	0.005	$824,094
Abaloparatide	$15,555	0.066	0.007	$235,430

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 27, along with net price per pen.

Table 27. 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
Teriparatide (cost per pen)	$1,866.34	$238.47	$329.77	$421.07
Abaloparatide (cost per pen)	$1,186.25	$379.30	$521.42	$663.55

QALY: quality-adjusted life year

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.[98] 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, whereas Tosteson et al. 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.[94,99-103] We found one 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.[104] 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).

6.2 Value-Based Benchmark Prices

Our value-based benchmark prices for abaloparatide and teriparatide are presented in Table 28. As noted in the initial ICER methods document (http://icer-review.org/wpcontent/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINALcorrected-8-22-1.pdf), the value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY gained.

For both abaloparatide and teriparatide, the discounts required to meet both threshold prices are greater than the current discounts from WAC (assumed 27% for abaloparatide, 38% for teriparatide).

Table 28. Value-based Benchmark Prices for Abaloparatide and Teriparatide for Osteoporosis Treatment in Postmenopausal Women

Drug Name	WAC per Pen	Net Price* per Pen	Pen Price to Achieve $100,000/QALY	Pen Price to Achieve $150,000/QALY	Discount from WAC to reach $100,000 and $150,000/QALY Threshold	Average Net Price Within Benchmark Range?
Teriparatide	$2,997.90	$1,866.34‡	$329.77	$421.07	86% to 89%	No
Abaloparatide	$1,625.00	$1,186.25†	$521.42	$663.55	59% to 68%	No

QALY: quality-adjusted life year, WAC: wholesale acquisition cost, WTP: willingness to pay

*Net price is the estimated price after discounts and rebates from WAC.

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

‡ Price per pen including 38% discount

6.3 Potential Budget Impact

We used the cost-effectiveness model to estimate the potential total budgetary impact of abaloparatide for postmenopausal women with osteoporosis and high risk of fracture. We used the WAC, an estimate of discounted WAC, and the three threshold prices for abaloparatide in our estimates of budget impact. Teriparatide was not included in this analysis because of its 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 therapy.

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, 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.[32] Of those receiving treatment, 66% were diagnosed with osteoporosis while the remainder were treated for osteopenia.[32] 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.[32] This high-risk population was assumed to be eligible to receive treatment with abaloparatide. 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, when we evaluate a new drug or device that would take market share from one or more drugs, we calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. We assumed that abaloparatide would take market shares from teriparatide and zoledronic acid in a ratio of 80:20 (i.e., abaloparatide would take 80% from teriparatide and 20% from zoledronic acid). We tested the potential budget impact of abaloparatide by assuming different unit price points (WAC, discounted WAC, and the three cost-effectiveness threshold prices for abaloparatide) against the combination of the discounted WAC for teriparatide and the average generic price for zoledronic acid.

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, 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 29.

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 29. 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 30 illustrates the per-patient budget impact results in more detail. Costs for abaloparatide were calculated using the WAC, discounted WAC, and 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 WAC, discounted WAC and across all three cost-effectiveness thresholds, ranging from approximately -$120 per patient using the WAC price ($1,625), to approximately -$10,500 per patient using the price to achieve $50,000 per QALY ($379).

Table 30. 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	$13,952	$10,290	$5,928	$4,742	$3,556
Teriparatide + Zoledronic acid* (Discounted WAC Only)	$14,072				
Difference	-$120†	-$3,782†	-$8,144†	-$9,330†	-$10,516†

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

†Indicates cost-saving

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

6.4 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 a 38% and 27% discount on list 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, varying the ramp-up time to full zoledronic acid efficacy, 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, 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 incremental 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 attempted to mitigate the influence of hip fracture 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, our base-case cost and cost-effectiveness results for anabolics reflect our current assumptions about drug prices. 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, our budget impact analysis for abaloparatide indicates that its use in place of teriparatide and zoledronic acid is not likely to generate access or affordability alerts when using WAC, discounted WAC, or the prices to achieve cost-effectiveness thresholds of $150,000 per QALY or lower.

****

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. Amgen And UCB Announce Top-Line Phase 3 Data From Active-Comparator Study Of EVENITY™ (Romosozumab) In Postmenopausal Women With Osteoporosis [press release]. May 21 2017.
5. 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.
6. 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.
7. 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.
8. 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.
9. Qaseem A, Forciea M, McLean RM, Denberg TD, for the Clinical Guidelines Committee of the American College of P. Treatment of low bone density or osteoporosis to prevent fractures in men and women: A clinical practice guideline update from the american college of physicians. *Annals of internal medicine.* 2017.
10. 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.
11. 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.
12. 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.
13. 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.

14. 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.
15. 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.
16. National Osteoporosis Foundation. Bone Health Index Survey: Final Report - September 2016. 2016.
17. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. *N Engl J Med.* 2016;375(16):1532-1543.
18. 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.
19. 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.
20. 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.
21. Prevrhal S, Krege JH, Chen P, Genant H, Black DM. Teriparatide vertebral fracture risk reduction determined by quantitative and qualitative radiographic assessment. *Current medical research and opinion.* 2009;25(4):921-928.
22. Burge RT, Disch DP, Gelwicks S, Zhang X, Krege JH. Hip and other fragility fracture incidence in real-world teriparatide-treated patients in the United States. *Osteoporos Int.* 2017;28(3):799-809.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. SSR Health. US Brand Rx Net Price. 2016.
31. 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.

32. 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.
33. 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.
34. 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.
35. US Preventive Services Task Force. Screening for osteoporosis: U.s. preventive services task force recommendation statement. *Annals of internal medicine.* 2011;154(5):356-364.
36. 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.
37. National Quality Measures Clearinghouse. Osteoporosis: percentage of women age 50 to 85 who suffered a fracture and who either had a bone mineral density test or received a prescription for a drug to treat osteoporosis. 2015.
38. 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.
39. Aetna. 2017 Prescription Drug Search. 2017; https://rxtools.aetnamedicare.com/PlanCompare/indeptools2017/Tools/FormularySearch/FormularySearch.aspx. Accessed March 29, 2017.
40. 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.
41. 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.
42. 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.
43. 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 June 14, 2017.
44. Humana. Provider Drug List Search. 2017; http://apps.humana.com/UnsecuredDrugListSearch/Search.aspx. Accessed June 14, 2017.
45. 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.
46. 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.
47. Anthem Blue Cross. Prior Authorization Criteria. 2017; https://www11.anthem.com/ca/provider/f0/s0/t0/pw_e234981.pdf. Accessed March 29, 2017.

48. 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.
49. 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.
50. 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.
51. Humana. Forteo (teriparatide) Pharmacy Coverage Policy (Medicare and Puerto Rico). Vol 20172016.
52. 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.
53. Humana. Reclast (zoledronic acid) Pharmacy Coverage Policy (Medicare, Exchanges, Puerto Rico, Commercial). 2016.
54. Humana. Zometa (zoledronic acid) Pharmacy Coverage Policy (Medicare, Exchanges, Puerto Rico, Commercial). 2017.
55. Anthem Blue Cross. Individual Select Drug List (Searchable). 2017; https://www11.anthem.com/ca/pharmacyinformation/. Accessed June 14, 2017.
56. 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.
57. 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.
58. 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.
59. 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.
60. 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.
61. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
62. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008). The Cochrane Collaboration; 2008.
63. 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.
64. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.

65. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(7521):897-900.
66. 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.
67. Black DM, Rosen CJ. Postmenopausal Osteoporosis. *New England Journal of Medicine.* 2016;374(3):254-262.
68. Langdahl BL, Rajzbaum G, Jakob F, et al. Reduction in fracture rate and back pain and increased quality of life in postmenopausal women treated with teriparatide: 18-month data from the European Forsteo Observational Study (EFOS). *Calcified tissue international.* 2009;85(6):484-493.
69. Yu S, Burge RT, Foster SA, Gelwicks S, Meadows ES. The impact of teriparatide adherence and persistence on fracture outcomes. *Osteoporos Int.* 2012;23(3):1103-1113.
70. Silverman S, Miller P, Sebba A, et al. The Direct Assessment of Nonvertebral Fractures in Community Experience (DANCE) study: 2-year nonvertebral fragility fracture results. *Osteoporosis International.* 2013;24(8):2309-2317.
71. Kendler D, Zerbini C, Russo L, et al. Effects of 24 Months Treatment of Teriparatide Compared with Risedronate on New Fractures in Postmenopausal Women with Severe Osteoporosis: a Randomised, Double-Dummy Clinical Trial (VERO). Paper presented at: World Congress on Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases2017; Florence, Italy.
72. 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.
73. 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.
74. Cefalu CA. Is bone mineral density predictive of fracture risk reduction? *Current medical research and opinion.* 2004;20(3):341-349.
75. Miller PD. Bone density and markers of bone turnover in predicting fracture risk and how changes in these measures predict fracture risk reduction. *Current Osteoporosis Reports.* 2005;3(3):103-110.
76. Seeman E. Is a change in bone mineral density a sensitive and specific surrogate of anti-fracture efficacy? *Bone.* 2007;41(3):308-317.
77. 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.
78. 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.
79. 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.
80. 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.
81. Centers for Disease Control and Prevention. United States Life Tables, 2008. https://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_03.pdf.
82. Neumann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. *Cost-effectiveness in health and medicine.* Oxford University Press; 2016.

83. Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2012;27(2):243-254.
84. Black DM, Reid IR, Cauley JA, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2015;30(5):934-944.
85. 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.
86. 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.
87. Kanis JA, Johnell O, Oden A, et al. The risk and burden of vertebral fractures in Sweden. *Osteoporos Int.* 2004;15(1):20-26.
88. 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.
89. 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.
90. 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.
91. Redbook Online. 2017.
92. Radius Health. TYMLOS™ and 1q 2017 Financial Results Update. [Investor presentation]. 2017; http://edge.media-server.com/m/p/z5woypf3. Accessed 38.
93. Bonafede M, Shi N, Viswanathan HN, Yurgin N. PMS13 OSTEOPOROSIS-RELATED FRACTURE COSTS AMONG FEMALE COMMERCIALLY INSURED AND MEDICARE PATIENTS. *Value in Health.* 2011;14(3):A125.
94. 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.
95. Insinga R. Administration Costs of Denosumab and Zoledronic Acid for Postmenopausal Osteoporosis. *Am J Pharm Benefits.* 2016;8(3):e42-e47.
96. Amgen and UCB Announce U.S. FDA Accepatance of Biologics License Application for Romosozumab [press release]. 2016.
97. 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.
98. 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.

99. 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.
100. 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.
101. 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.
102. 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.
103. 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.
104. 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.
105. 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).
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.

	#	Checklist item
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

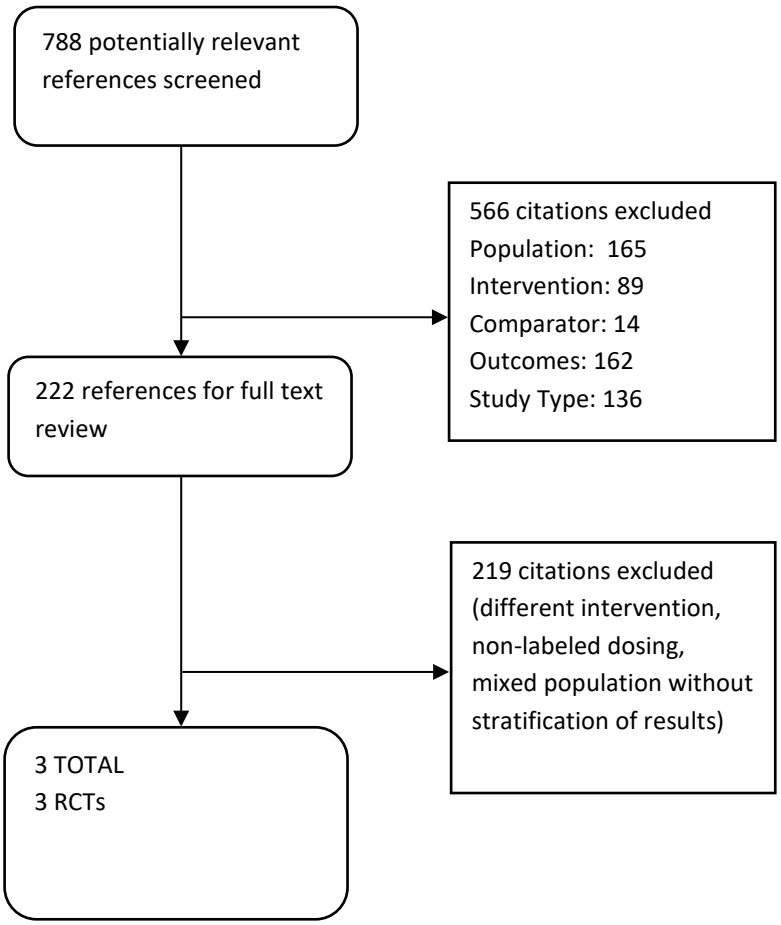
Table A3. Cochrane Central Register of Controlled Trials search, January 24, 2017 (via Ovid)

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. California Health Exchange and Medicaid Coverage Policies

Table B1. Representative Medi-Cal and Silver-Tier Covered California Coverage Policies for Abaloparatide, 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
Abaloparatide					
Tier	-	Non-formulary	Specialty	-	-
ST	-	-	-	-	-
PA	-	-	-	-	-
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[25]

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[24]

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[23]

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[27]

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[26]

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[66]

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)[105] 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[19]	Fracture Prevention Trial	Teriparatide 20 mcg SC QD Placebo SC QD	541 544	21	-	100% vertebral
Abaloparatide						
Miller 2016[18]	ACTIVE	Abaloparatide 80 mcg SC QD Teriparatide 20 mcg SC QD Placebo SC QD	824 818 821	18	-2.5 to -5.0	24% vertebral 63% any
Romosozumab						
Cosman 2016[17]	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[20]	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[19]	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[18]	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[17]	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[20]	HORIZON	Female Postmenopausal Ages 65-89 years T-score -2.5 to -3.5	Use of PTH or sodium fluoride Recent use of corticosteroids CrCl < 30 ml/min	Vitamin D 400-1200 IU daily Calcium 1000 – 1500 mg daily

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[19]	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[18]	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[17]	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[20]	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[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Abaloparatide								
Miller 2016[18]	Yes	Yes	Yes*	Yes	Yes	Yes	Yes	Good vs. placebo
Romosozumab								
Cosman 2016[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Key comparator: Zoledronic acid								
Black 2007[20]	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[19] **21 months**	Teriparatide Placebo	22 (5.0%) 64 (14.3%)	14 (2.6%) 30 (5.5%)	1 (0.2%) 4 (0.7%)	7 (1.3%) 13 (2.4%)	NR	NR
Prevrhal 2009[21]	Teriparatide Placebo	8 (1.8%)* 51 (11.4%)					
Abaloparatide							
Miller 2016[18] **18 months**	Abaloparatide Teriparatide Placebo	4 (0.6%) 6 (0.8%) 30 (4.2%)	18 (2.7%) 24 (3.3%) 33 (4.7%)	0 (0%) 0 (0%) 2 (0.2%)	7 (0.8%) 17 (2.1% 15 (1.8%)	10 (1.5%) 23 (3.1%) 34 (6.2%)	27 (4.0%) 35 (4.8%) 49 (8.3%)
Romosozumab							
Cosman 2016[17] **12 months**	Romosozumab Placebo	16 (0.5%) 59 (1.8%)	56 (1.6%) 75 (2.1%)	7 (0.2%) 13 (0.4%)	NR	38 (1.1%) 63 (1.8%)	58 (1.6%) 90 (2.5%)
Key comparator: Zoledronic acid							
Black 2007[20] **36 months**	Zoledronic acid Placebo	92 (3.3%) 310 (10.9%)	292 (8.0%) 388 (10.7%)	52 (1.4%) 88 (2.5%)	NR	NR	308 (8.4%) 456 (12.8%)

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

* Using alternative definition for incident vertebral fractures: decrease in height of at least 20% and 4 mm using quantitative morphometry plus an increase in grade by the semiquantitative assessment. The primary analysis (Neer 2001) used a single reader increase in grade using the semiquantitative assessment of vertebral fracture.

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[19]	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)
Prevrhal 2009[21]	Teriparatide Placebo	0.16 (0.08-0.33)* 1 (ref)				
Abaloparatide						
Miller 2016[18]	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[17]	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[20]	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

* Using alternative definition for incident vertebral fractures: decrease in height of at least 20% and 4 mm using quantitative morphometry plus an increase in grade by the semiquantitative assessment. The primary analysis (Neer 2001) used a single reader increase in grade using the semiquantitative assessment of vertebral fracture.

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[19] **21 months**	Teriparatide Placebo	+9.7% +1.1%	+2.8% -0.7%	+2.6% -1.0%
Abaloparatide				
Miller 2016[18] **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[17] **12 months**	Romosozumab Placebo	13.3 % difference	5.9% difference	6.9% difference
Key comparator: Zoledronic acid				
Black 2007[20] **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 Morphometric Vertebral Fractures, Excluding Open-Label Teriparatide Arm from ACTIVE Trial

Abaloparatide (80 mcg)			
0.91 (0.22 – 3.20)	**Teriparatide (20 mcg)**		
0.45 (0.13 – 1.21)	0.51 (0.22 – 1.00)	**Zoledronic Acid (5 mg)**	
0.13 **(0.04 – 0.34)**	**0.15** **(0.07 – 0.28)**	**0.30** **(0.24 – 0.37)**	**Placebo**

Fixed-effects model; resdev = 5.352, DIC = 43.663

Legend: Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.

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

Teriparatide (20 mcg)			
0.81 (0.34 – 1.87)	Abaloparatide (80 mcg)		
0.62 (0.31 – 1.09)	0.75 (0.41 – 1.30)	Zoledronic Acid (5 mg)	
0.45 (0.23 – 0.81)	**0.55 (0.31 – 0.95)**	**0.75 (0.64 – 0.86)**	Placebo

Fixed-effects model; resdev = 5.387, DIC = 46.775

Legend: Each box represents the estimated rate ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs: the drug at the top of the column compared to the drug at the right of the row. Estimates in bold signify that the 95% credible interval does not contain 1.

Table E10. NMA Sensitivity Analyses: Morphometric Vertebral Fracture Comparisons to Placebo

Drug	Study Publication RR (95% CrI)	Fixed Effects RR (95% CrI)	Random Effects, Vague Priors RR (95% CrI)	Random Effects, Informative Priors RR (95% CrI)	Sensitivity Analysis Excluding Teriparatide Arm of ACTIVE Trial, Fixed Effects RR (95% CrI)	Sensitivity Analysis Using Neer 2001 Teriparatide Data, Fixed Effects, RR (95% CrI)
Abaloparatide (80 mcg)	**0.14 (0.05 – 0.39)**	**0.13 (0.03 – 0.33)**	**0.13 (0.01 – 0.95)**	**0.13 (0.03 – 0.38)**	**0.13 (0.04 – 0.34)**	**0.14 (0.04 – 0.35)**
Teriparatide* (20 mcg)	**0.16 (0.08 – 0.33)**	**0.17 (0.09 – 0.29)**	**0.17 (0.03 – 0.75)**	**0.17 (0.09 – 0.34)**	**0.15 (0.07 – 0.28)**	**0.30 (0.19 – 0.45)**
Zoledronic Acid (5 mg)	**0.30 (0.24 – 0.38)**	**0.30 (0.24 – 0.37)**	0.30 (0.03 – 1.94)	**0.30 (0.15 – 0.55)**	**0.30 (0.24 – 0.37)**	**0.30 (0.24 – 0.38)**

CrI: credible interval, RR: relative risk

*Teriparatide results were calculated using Prevrhal, 2009[21] with the exception of the final column, which used data from Neer, 2001.[19]

Estimates in bold signify that the 95% credible interval does not contain 1.

Table E11. NMA Sensitivity Analyses: Non-Vertebral Fracture Comparisons to Placebo

Drug	Study Publication RR (95% CrI)	Fixed Effects RR (95% CrI)	Random Effects, Vague Priors RR (95% CrI)	Random Effects, Informative Priors RR (95% CrI)	Sensitivity Analysis Excluding Teriparatide Arm of ACTIVE Trial, Fixed Effects RR (95% CrI)
Abaloparatide (80 mcg)	0.57* (0.32 – 1.00)	**0.51 (0.28 – 0.85)**	0.50 (0.07 – 2.80)	0.50 (0.23 – 1.04)	**0.55 (0.31 – 0.95)**
Teriparatide (20 mcg)	**0.47 (0.25 – 0.88)**	**0.61 (0.41 – 0.88)**	0.60 (0.13 – 2.32)	0.60 (0.34 – 1.04)	**0.45 (0.23 – 0.81)**
Zoledronic Acid (5 mg)	**0.75* (0.64 – 0.87)**	**0.75 (0.64 – 0.87)**	0.75 (0.10 – 4.08)	0.75 (0.40 – 1.36)	**0.75 (0.64 – 0.86)**

CrI: credible interval, NR: not reported, RR: relative risk

*Denotes use of hazard ratios instead of relative risks; RRs were not reported in the trial publication.

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		Teriparatide	
	Deterministic	Credible Range (from PSA)	Deterministic	Credible Range (from PSA)	Deterministic	Credible Range (from PSA)
Total Cost	$25,465	($20,844 - $31,176)	$47,525	($40,081 - $56,361)	$68,905	($58,313 - $80,110)
Anabolic Cost	--		$27,574	($22,185 - $33,303)	$47,159	($37,791 - $56,803)
Zoledronic Acid Cost	$2,498	($2,150 - $2,895)	$2,243	($1,931 - $2,600)	$2,243	($1,931 - $2,600)
Hip Fracture Cost	$7,276	($5,058 - $9,910)	$5,708	($3,594 - $8,877)	$6,211	($4,029 - $9,120)
Clinical Vert Fracture Cost	$1,202	($863 - $1,617)	$806	($510 - $1,303)	$864	($591 - $1,248)
Other Non-Vertebral Fracture Cost	$5,084	($3,896 - $6,538)	$4,147	($2,739 - $6,201)	$4,556	($3,164 - $6,348)
Post-Fracture Cost	$9,404	($6,636 - $13,116)	$7,048	($4,209 - $11,550)	$7,871	($5,064 - $11,849)
Total QALYs	8.93	(7.54 - 10.13)	9.00	(7.60 - 10.21)	8.98	(7.58 - 10.18)
Pre-Fracture QALYs	6.29	(5.16 - 7.28)	6.96	(5.62 - 8.14)	6.72	(5.50 - 7.81)
Hip Fracture QALYs	0.08	(0.06 - 0.12)	0.07	(0.04 - 0.11)	0.07	(0.04 - 0.11)
Vert Fracture QALYs	0.05	(0.04 - 0.07)	0.04	(0.02 - 0.06)	0.04	(0.03 - 0.05)
Other Fracture QALYs	0.27	(0.20 - 0.34)	0.22	(0.14 - 0.33)	0.24	(0.16 - 0.33)
Post-Fracture QALYs	2.24	(1.81 - 2.67)	1.72	(1.23 - 2.29)	1.91	(1.46 - 2.41)
Lifetime Cumulative Fracture Probabilities						
Hip Fractures	0.24	(0.18 - 0.31)	0.19	(0.13 - 0.28)	0.21	(0.15 - 0.29)
Clinical Vert Fractures	0.18	(0.15 - 0.22)	0.13	(0.09 - 0.19)	0.14	(0.11 - 0.17)
Other Non-Vertebral Fractures	0.54	(0.46 - 0.63)	0.46	(0.33 - 0.64)	0.50	(0.38 - 0.64)

Table F2. Detailed Incremental Results versus Zoledronic Acid

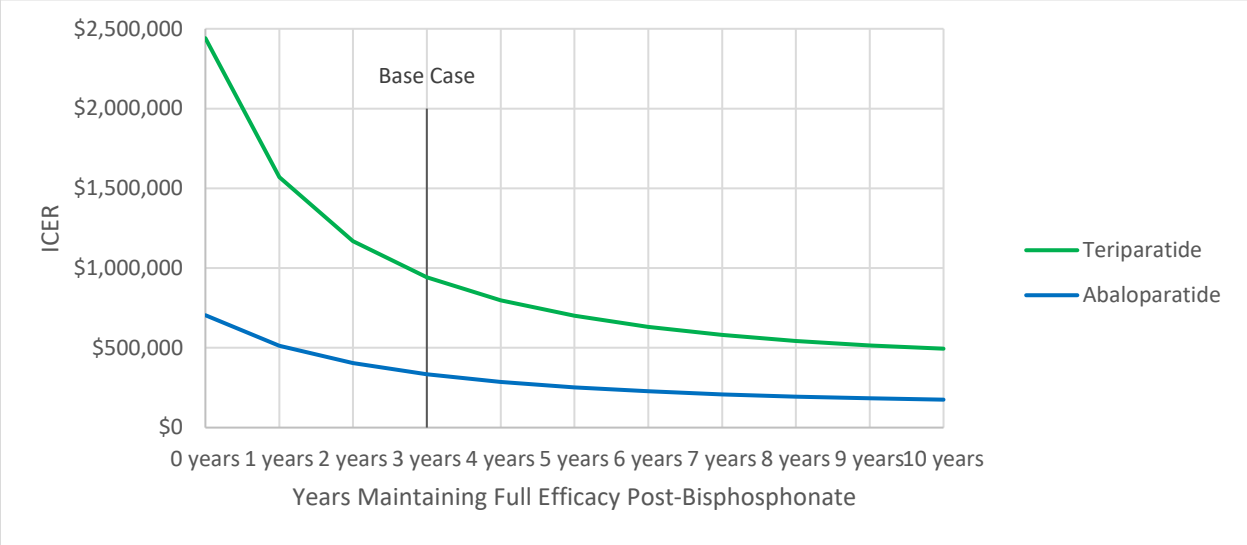
	Abaloparatide		Teriparatide	
	Deterministic	Credible Range (from PSA)	Deterministic	Credible Range (from PSA)
ICER	$333,892	(-$1,183,554 - $2,480,241)	$941,537	(-$4,498,030 - $7,758,067)
Incremental Cost	$22,061	($14,728 - $30,542)	$43,440	($33,081 - $54,238)
Anabolic Cost	$27,574	($22,185 - $33,303)	$47,159	($37,791 - $56,803)
Zoledronic Acid Cost	-$255	(-$295 - -$219)	-$255	(-$295 - -$219)
Hip Fracture Cost	-$1,568	(-$3,775 - $1,023)	-$1,065	(-$3,047 - $1,046)
Clinical Vert Fracture Cost	-$396	(-$698 - $37)	-$339	(-$572 - -$94)
Other Non-Vertebral Fracture Cost	-$937	(-$2,340 - $836)	-$528	(-$1,747 - $824)
Post-Fracture Cost	-$2,356	(-$5,941 - $1,771)	-$1,533	(-$4,733 - $1,846)
Incremental QALYs	0.07	(-0.01 - 0.15)	0.05	(-0.01 - 0.11)
Pre-Fracture QALYs	0.68	(0.05 - 1.22)	0.43	(-0.04 - 0.87)
Hip Fracture QALYs	-0.02	(-0.05 - 0.01)	-0.01	(-0.04 - 0.01)
Vert Fracture QALYs	-0.02	(-0.03 - 0.00)	-0.02	(-0.03 - 0.00)
Other Fracture QALYs	-0.05	(-0.12 - 0.04)	-0.03	(-0.09 - 0.04)
Post-Fracture QALYs	-0.52	(-0.97 - -0.01)	-0.33	(-0.68 - 0.05)
Lifetime Cumulative Fracture Probabilities				
Hip Fractures	-0.05	(-0.11 - 0.03)	-0.03	(-0.09 - 0.03)
Clinical Vert Fractures	-0.05	(-0.08 - 0.00)	-0.05	(-0.07 - -0.01)
Other Non-vertebral Fractures	-0.08	(-0.21 - 0.09)	-0.05	(-0.16 - 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.

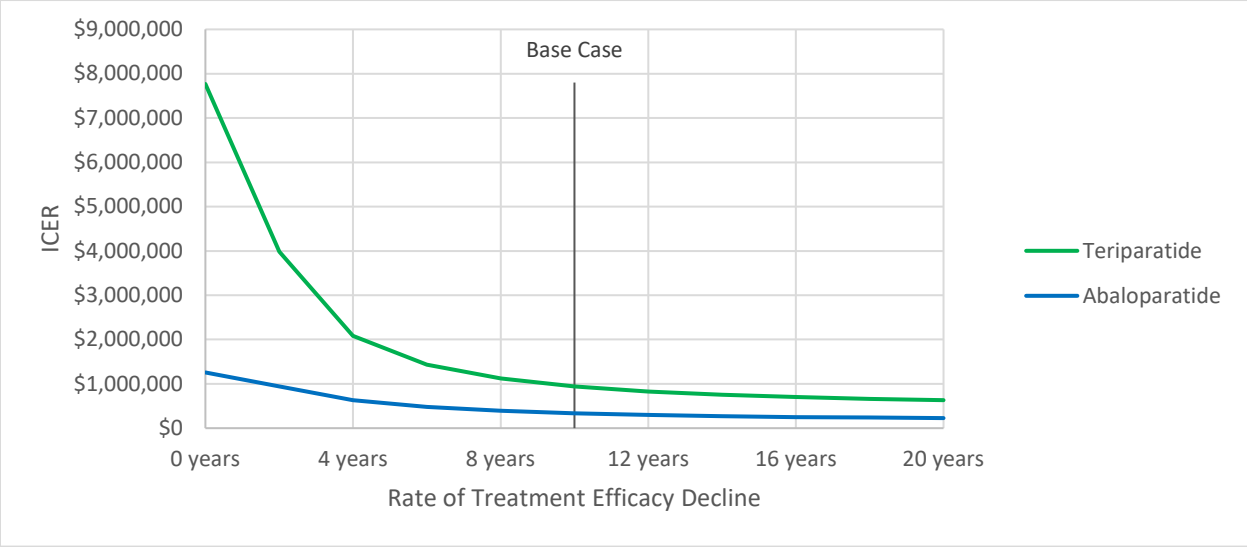
Figure F1. Results of Anabolic Treatment Efficacy Maintenance Scenario Analysis



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.

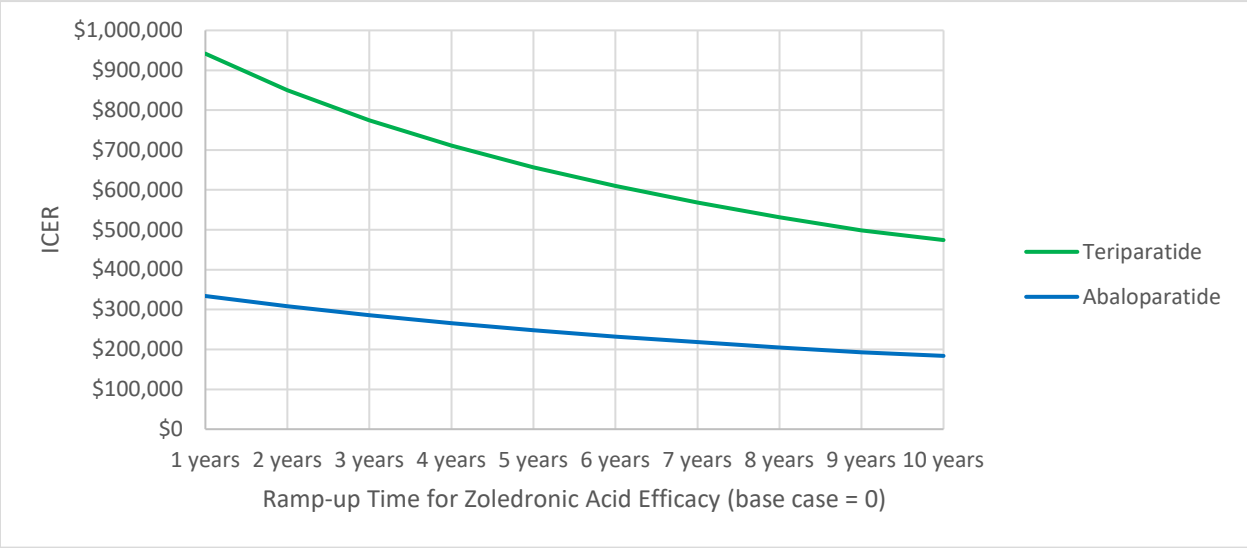
Figure F2. Number of Years of Efficacy Decline Duration Scenarios



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. We calculated hip fracture relative risk estimates based on the ratio of hip to non-vertebral fracture relative risks in the HORIZON trial, similar to the base case approach. This scenario resulted in a small decline in incremental QALYs and small increase in cost for abaloparatide, and an increase in incremental QALYs with decreased cost for teriparatide.

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	0.30 (0.24 – 0.37)	0.75 (0.64 – 0.86)
Teriparatide 20 mcg	0.15 (0.07 – 0.28)	0.45 (0.23 – 0.81)
Abaloparatide 80 mcg	0.13 (0.04 – 0.34)	0.55 (0.31 – 0.95)

RR: relative risk

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

Regimen	Cost	QALYs	Life Years
Zoledronic Acid	$25,465	8.933	12.188
Teriparatide	$66,010	9.008	12.196
Abaloparatide	$48,183	8.992	12.194

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
Teriparatide	$40,545	0.076	0.008	$535,758
Abaloparatide	$22,718	0.060	0.006	$380,332

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

Including Zoledronic Acid-Associated Infusion Reaction

Although we found little evidence of significant differences in adverse event rates between modeled comparators and placebo, multiple clinical stakeholders indicated that infusion reactions following zoledronic acid administration were a potentially significant adverse event that warranted consideration. In this scenario, we used the approach employed by the National Institute for Health and Care Excellence (NICE) in their systematic review and cost-effectiveness analysis of bisphosphonates.[23] Briefly, they assumed a disutility of 0.30 for 3 days for flu-like symptoms associated with IV bisphosphonates, which is equivalent to a QALY loss of 0.005. They applied this

as a fixed QALY decrement at the start of the model without adjustment for baseline utility. The rate of influenza-like symptoms was assumed to be the differential rate of pyrexia reported in the HORIZON-PFT study (14%).[20] This small disutility for zoledronic acid had little impact on our model results.

Table F6. Results of Scenario Analysis Including Zoledronic Acid-Associated Infusion Reaction

	Cost	QALYs	Life Years
Zoledronic Acid	$25,465	8.932	12.188
Teriparatide	$68,905	8.979	12.193
Abaloparatide	$47,525	8.999	12.195
QALY: quality-adjusted life year			

Table F7. Pairwise Results of Anabolic Drugs Compared to Zoledronic Acid, Including Zoledronic Acid-Associated Infusion Reaction

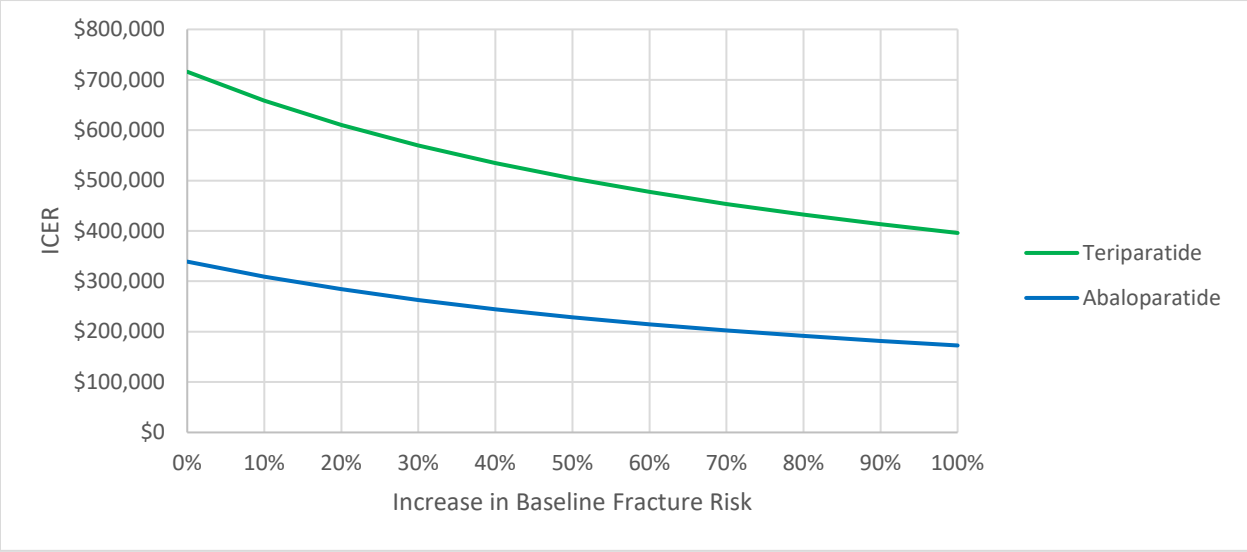
	Incr. Cost	Incr. QALYs	Incr. LYs	ICER
Teriparatide	$43,440	0.047	0.005	$927,466
Abaloparatide	$22,061	0.067	0.007	$330,391

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

Baseline Fracture Risk in Higher-Risk Patient Groups who are Intolerant of Zoledronic Acid

In this scenario, we set zoledronic acid relative risks estimates to 1, set the zoledronic acid costs to zero, "turned off" post-anabolic zoledronic acid treatment, and modeled a range of increased baseline fracture probabilities to explore the impacts of anabolics on high risk patients who cannot tolerate zoledronic acid either as primary or subsequent therapy. Even at 100% increased baseline fracture probability, the ICERs for abaloparatide and teriparatide did not reach the $150,000 per QALY threshold.

Figure F4. Baseline Fracture Risk Scenarios in Higher-Risk Groups Intolerant of Zoledronic Acid



Inclusion of a Disutility for Morphometric Vertebral Fractures

A number of stakeholders indicated that patients who have morphometric fractures experience a small disutility, and that we should include this in our model. In this scenario analysis, we added a morphometric utility multiplier and varied it over a wide range of values, from no disutility (multiplier = 1) down to an extreme value of 0.8. Because this was applied to all comparators, and because the relative risk for vertebral fracture were generally similar among comparators, the differences in utilities were largely "washed out", and had little impact on ICER results.

Figure F5. Inclusion of a Disutility for Morphometric Vertebral Fractures