Anabolic Therapies for Osteoporosis: Effectiveness and Value

Final Background and Scope
January 9, 2017

Stakeholder Input:

This scoping document was developed with substantial input from several osteoporosis patient advocacy organizations. ICER also engaged with and received detailed input from relevant specialty societies, practicing endocrinologists, geriatricians, general internists, pharmaceutical manufacturers, and payers to inform the research direction outlined in this scope. Based on feedback from the above stakeholders, ICER has decided to focus on anabolic agents for osteoporosis; denosumab (Prolia®, Amgen, Inc.), an anti-resorptive agent that was listed in the topic announcement for this review, has thus been removed from the list of comparator agents.

The Final Background and Scope reflects feedback gathered during a three-week public comment period. Based on stakeholder input, the background section has been updated with additional context about the number of Americans with osteoporosis, revised language about the first-line therapies used by most patients, and updated language about the negative health consequences of osteoporosis. The description of romosozumab has been updated to reflect its anti-resorptive properties, and additional context has been added about the patients that may be candidates for first-line use of anabolic agents. The description of comparators has been updated to include rationale for the planned comparison of anabolic agents to bisphosphonates. Hypercalcemia has been added to the list of key harms; although hypocalcemia is not associated with anabolic agents, it is an important potential harm of bisphosphonate therapy and as such remains in the list of key harms. The comparative value section has been updated with additional detail about the time horizons for the cost-effectiveness analysis, and to note that ICER will perform a scenario analysis that includes productivity costs if data permits. ICER looks forward to continued engagement with stakeholders throughout its review of anabolic treatments for osteoporosis.

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 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 suffer 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]

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

medication from the bisphosphonate class of drugs. If patients are unable to tolerate oral bisphosphonates, then IV bisphosphonates are generally recommended.

Osteoporotic fractures can lead to pain, disability, and death. Even asymptomatic vertebral fractures may result in loss of height and pronounced curving of the spine (kyphosis) that interfere with activities and make breathing difficult. Patients have become increasingly concerned about two adverse events associated with use of bisphosphonate therapy: osteonecrosis of the jaw and atypical femoral fractures. These concerns may partially explain the 50% decrease in the use of bisphosphonate therapy from 2008 to 2012.[4] 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.

The goal of treatment is to prevent the fragility fractures associated with osteoporosis: hip, spine, and wrist fractures. There are two emerging anabolic (i.e., bone-building) therapies for osteoporosis: abaloparatide (Radius Health, Inc.) and romosozumab (Amgen, Inc. and UCB, Inc.); romosozumab also decreases bone resorption.[5] The only other anabolic agent is teriparatide (Forteo®, Eli Lilly and Co.), which acts through a similar mechanism to abaloparatide. All other FDA approved agents for osteoporosis are anti-resorptive (i.e., they decrease the breakdown of bone). This assessment will focus on these three anabolic agents. Each of the three drugs listed above are delivered via subcutaneous injection. Anabolic therapies may decrease the risk of fracture more rapidly than anti-resorptive therapies, and so may be particularly appropriate for first-line use in patients at high risk for fragility fractures in the near term.

Report Aim:

This project will evaluate the health and economic outcomes of anabolic treatments for osteoporosis. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

Scope of the Assessment:

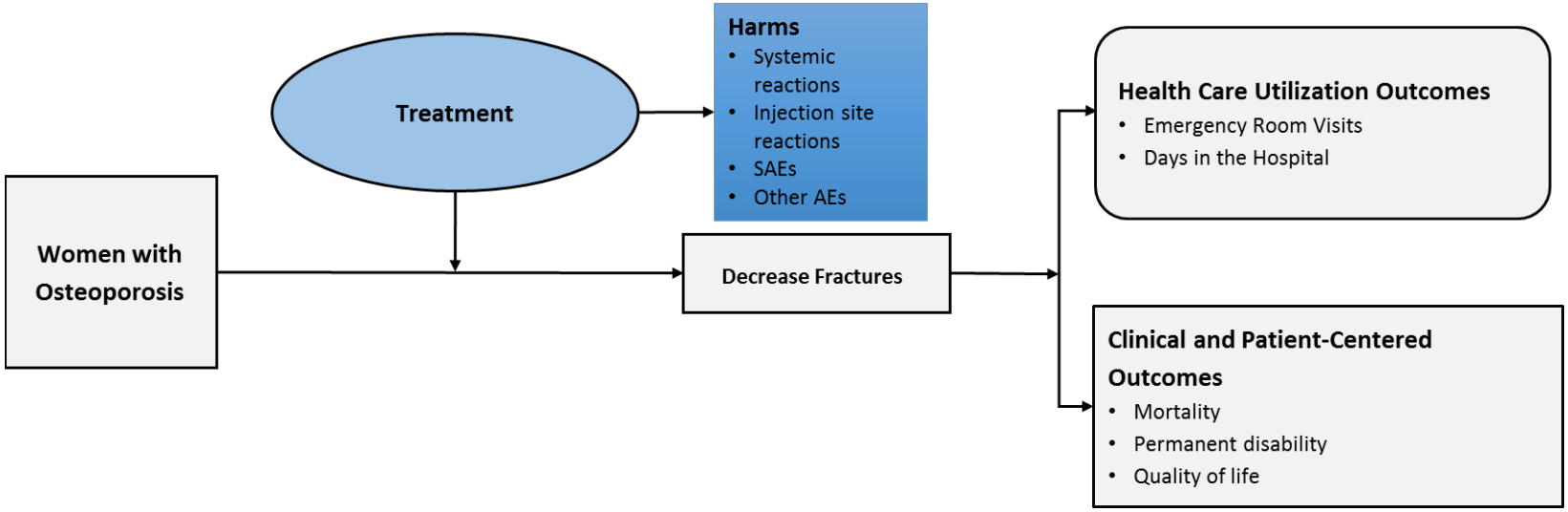
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Wherever possible, we will seek out head-to-head studies of these interventions. In the absence of head-to-head studies, we will use placebo-controlled studies and derive indirect comparisons from a network meta-analysis when appropriate. High-quality observational studies will be included.

Analytic Framework:

The general analytic framework for assessment of therapies for osteoporosis is depicted in Figure 1 on the following page.

Figure 1. Analytic Framework: Anabolic Therapies for Osteoporosis



AE: adverse event, SAE: serious adverse event

Populations

The population of focus for the review is post-menopausal women with an indication for treatment to prevent osteoporotic fractures.

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

Comparators

Data permitting, we intend to compare all the agents to each other and to bisphosphonate therapy. Comparing the agents with bisphosphonates may allow us to evaluate the relative incremental benefits and harms of these agents when used first line in patients at various short-term risks 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. Next in importance is clinical vertebral fractures, which are compression fractures of the spine that cause pain. Finally, all fragility fractures and all fractures will be considered as outcomes. Changes in bone mineral density, bone turnover markers, and radiographic vertebral fractures will be considered as surrogate outcomes.

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

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

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

<u>Surrogate Outcomes</u>
Bone mineral density
Bone turnover markers
Radiographic vertebral fractures

Timing

Evidence on intervention effectiveness will be derived from studies of at least one year's duration and evidence on harms from studies of at least three month's duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Simulation Models Focusing on Comparative Value:

Injectable medications are relatively expensive compared to oral bisphosphonate treatment. Patient advocacy organizations noted that insurance coverage of newer, injectable therapies is highly variable, and may make it more difficult for patients to access treatment. As a complement to the evidence review, we will develop a simulation model to assess the lifetime cost-effectiveness of the treatments of interest relative to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of osteoporosis. The base case analysis will take a health-system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity losses will be considered in a separate analysis. The target population will consist of post-menopausal women with an indication for treatment to prevent osteoporotic fractures. The model will consist of health states including osteoporosis without fracture, hip fracture, vertebral fracture, other fracture (including wrist or tibia fracture), and death. A cohort of patients will transition between states during predetermined cycles (e.g. one year) over a lifetime time horizon, modeling patients from treatment initiation until death. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include the probability of fracture, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using network meta-analyses of hip fracture, vertebral fracture, and other fracture.

Health outcomes and costs will be dependent on time spent in each health state, fracture events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of numbers of fractures avoided, life-years and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state, including quality of life decrements for each fracture event and for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, fracture-related care, and serious adverse events. In addition, productivity losses will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, and cost per fracture avoided.

In an additional analysis, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. These budgetary impact analyses will assume varied “uptake” rates over a five-year period for the specific populations of interest. This analysis will indicate the relation between treatment price and level of uptake for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER’s methods for estimating product uptake and calculating potential budget impacts can be found at: https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/.

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. 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.
5. 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.