Amgen Response to ICER’s Draft Scoping Document on Anabolic Therapies for Osteoporosis

OVERVIEW

Amgen appreciates the opportunity to comment on ICER’s draft scoping document on anabolic therapies for osteoporosis. ICER proposes to compare two classes of osteoporosis treatments, bone-forming agents and antiresorptive agents, which have fundamentally different clinical contexts of use, and require very different considerations from a value assessment perspective.

Amgen strongly recommends that ICER’s scope reflect its intent to assess the health and economic outcomes of anabolic treatments for osteoporosis by focusing on the emerging bone-forming agents (romosozumab and abaloparatide) and the current bone-forming agent, teriparatide, and that ICER should not confound this assessment with a comparison to bisphosphonates. Bone-forming agents, including the sclerostin inhibitor romosozumab and the parathyroid hormone-related analogues abaloparatide and teriparatide, act via distinct mechanisms to build bone rapidly and reduce fractures over 1- to 1.5-year treatment courses, respectively. Antiresorptive agents, such as bisphosphonates, decrease bone resorption for more gradual BMD gains and fracture risk reduction over many years. Bone-forming agents are followed by an antiresorptive agent to protect the bone over time, given the chronic nature of osteoporosis. Bone-forming agents are currently used, and are expected to continue to be used, in patients at higher fracture risk than those treated with antiresorptive agents. Comparing bone-forming agents to antiresorptive agents would not adequately take into consideration this difference in treatment context, resulting in an erroneous analysis.

Our guidance on removal of bisphosphonates as a comparator is based on the below key points and recommendations:

- The population for this assessment should be the clinical population in which bone-forming agents are currently used and are expected to be used when additional bone-forming agents are made available; these patients can be identified as being at high risk for fracture in the near term (within 1 to 2 years). In contrast, patients typically treated with antiresorptive agents are those at lower risk for fracture. Attempts to generalize the population underestimates the value bone-forming agents bring to patients.

- The modeling timeframe for this assessment should be ≤ 2 years, reflective of the short-term use of bone-forming agents (treatment course of 1 to 2 years). In contrast, endpoints for antiresorptive agents were measured at 3+ years, reflecting long-term treatment courses seen in clinical practice. The use of non-overlapping timeframes will result in an inaccurate analysis if directly compared.

Another important consideration for this assessment, outlined under “Additional Considerations,” is the primary outcomes of interest, which should include all clinical fractures as well as morphometric vertebral fractures. We also offer input on secondary endpoints for assessment (BMD and bone turnover markers), persistence/adherence implications for modeling, and the use of subgroup clinical data as needed for efficacy assessments.

Details and evidence to support the recommendations are discussed below (also see Appendices for supplemental information and for the definitions of abbreviations used in this document).
KEY RECOMMENDATIONS

ICER’s assessment should compare bone-forming agents only to other bone-forming agents, and should not compare bone-forming agents to bisphosphonates, based on the following key points.

The population for this assessment should be the clinical population in which bone-forming agents are currently used and are expected to be used when additional bone-forming agents are made available; these patients can be identified as being at high risk for fracture in the near-term (within 1 to 2 years). In contrast, patients typically treated with antiresorptive agents are those at lower risk for fracture. Attempts to generalize the population underestimates the value bone-forming agents bring to patients.

Bone-forming agents are viewed as a distinct class of therapy by the medical community. Although ICER correctly notes treatment recommendations of a T-score ≤ -2.5 or 10-year fracture risk based on FRAX (hip fracture risk of ≥ 3% or major osteoporosis-related fracture risk of ≥ 20%), patients who receive the bone-forming agent teriparatide tend to be at a much higher fracture risk relative to patients treated with antiresorptive agents. In these higher-risk patients, bone-forming agents can improve impaired bone mass and structure allowing for more rapid offset of fracture risk, with subsequent sequencing to antiresorptive agents to help maintain or augment gains in new bone and continue fracture reduction over the long-term. Prior fracture history, lower BMD, and other co-morbidities are features reflecting higher fracture risk. Observational studies have shown that compared with patients treated with antiresorptive agents, patients treated with teriparatide demonstrate substantially higher baseline fracture rates—as high as 100% (Appendix A). Indeed, based on fracture history and other risk factors, the population in whom bone-forming agents are used can be characterized as patients at high near-term risk of fracture (i.e., within the next 1 to 2 years). Amgen is currently conducting research that will further inform identification of patients who are at high risk of a near-term fracture (Appendix B) and can provide additional information on this.

The modeling timeframe for this assessment should be ≤ 2 years, reflective of the short-term use of bone-forming agents (treatment course of 1 to 2 years). In contrast, endpoints for antiresorptive agents were measured at 3+ years, reflecting long-term treatment courses seen in clinical practice. The use of non-overlapping timeframes will result in an inaccurate analysis.

Bone-forming agents act quickly to reduce fracture risk over 1 to 2 years, as seen in treatment courses in pivotal fracture studies (Appendix C). In contrast, antiresorptive agents have been shown to have a maximal effect at about 3 to 4 years (Appendix D). Cost-effectiveness modeling should compare agents across their time-periods of use (e.g., 1 to 2 years for bone-forming agents). Given the reversibility of bone-forming agents and the chronic nature of osteoporosis, bone-forming agents are followed by antiresorptive agents in clinical practice. However, cost-effectiveness modeling of the various potential sequences of bone-forming agents to available antiresorptive agents over a lifetime horizon would require a separate assessment, with limited data available on the potential sequences that would be used in clinical practice.

In summary, ICER should remove bisphosphonates as a comparator in this assessment, as such a comparison to bone-forming agents would not adequately take into consideration the difference in treatment context, including patient population and timeframe of use, and result in an erroneous analysis (Appendix E).
ADDITIONAL CONSIDERATIONS

**Primary outcomes:** The primary outcomes of interest should broadly consider all osteoporotic clinical fractures in addition to morphometric vertebral fractures. Clinical osteoporotic fractures account for the majority of clinical and economic burden to patients and the health care system, including long-term impact on physical function and related disability, independence, caregiver support, work-related productivity/disability, quality of life, and mortality. Since hip fractures have a low incidence (~14% of all clinical fractures) and no studies of bone-forming agents have been powered to show significant effects on hip fracture, the primary outcome assessed should not only be the risk of hip fracture, but rather all relevant clinical fractures inclusive of hip, clinical vertebral, and other non-vertebral fragility fractures. Morphometric vertebral fractures are an additional important endpoint given the relationship between any morphometric vertebral fracture and future fracture and associated burden, such as chronic back pain and reduced quality of life.

**Secondary outcomes:** BMD offers a secondary endpoint for comparing bone-forming agents. BMD accounts for more than 80% of variation in bone strength, is established by regulators as an endpoint for bridging studies for additional indications once fracture risk reduction has been established, and has been proposed as a surrogate endpoint for regulatory approval of new agents by the FNIH Biomarkers Consortium’s Bone Quality Project. There are varying effects of bone-forming agents on BMD at the hip that may inform value assessments. Romosozumab has been shown to increase both hip and spine BMD more than teriparatide. In addition, bone turnover marker data will provide insight into the unique attributes of the individual drugs in the bone-forming class, and should be included in ICER’s assessment.

**Persistence/adherence implications:** Of further consideration for modeling fracture efficacy, bone-forming agents generally have better persistence/adherence. Teriparatide has high adherence and persistence rates in observational studies globally, likely due to the distinct higher-risk and more motivated population, coupled with a short duration of use. Many patients do not remain persistent with bisphosphonates for longer than 1 year. While we recommend against inclusion of bisphosphonates in this ICER assessment, it is important to note that, if included, the efficacy in bisphosphonate trials would have to be adjusted for modeling based upon expected persistence/adherence.

**Role of subgroup data for efficacy assessment:** The populations studied in the pivotal fracture trials may be broader than that in which a study drug is expected to be used. For example, the romosozumab FRAME study enrolled a relatively low-risk postmenopausal osteoporosis patient population because of the ethical consideration of not exposing higher-risk patients to placebo; subgroup data from higher-risk patients will be important to consider. Amgen can provide these data.

**CONCLUSION**

There is a significant unmet need in the field of osteoporosis with only 1 in 5 women being treated, even after a fragility fracture. Amgen strongly recommends that ICER consider the above key recommendations in their assessment of bone-forming agents. In particular, comparing bone-forming agents to bisphosphonates would not adequately take into consideration the difference in treatment context, which involves a distinct patient population, a distinct treatment timeframe, and a distinct treatment approach between bone-forming agents and bisphosphonates. If ICER’s assessment includes bisphosphonates as a comparator, this will result in an inaccurate representation of the value of bone-forming agents and compromise the clinical validity of the assessment. Taking the above recommendations into consideration will allow for more meaningful evaluation of this important class of therapy, and more accurately reflect the value that bone-forming agents bring to patients.
References


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December 20, 2016

RE: Response to ICER Draft Scoping Document (Anabolic Therapies for Osteoporosis)

Eli Lilly and Company appreciates the opportunity to respond to ICER’s draft background and scoping document titled ‘Anabolic Therapies for Osteoporosis: Effectiveness and Value’ released December 5, 2016. We believe that to be a sound value determination, efforts must be comprehensive and truly patient-centered. Thus we offer the following comments:

Population:
a) What is the exact patient profile of the PMO patient population in terms of BMD T-score, age, and prevalent fractures? Current US use of the available anabolic osteoporosis (OP) treatment is for patients at ‘high risk of fracture’ or have had a previous fragility fracture. Given the focus on anabolic OP treatments, will the population focus be on patients at high risk of fracture and particularly those that have had a previous fracture? Lilly recommends that the high risk population be defined as having osteoporotic fracture with increased age or lower BMD.

Interventions:
a) There are significant differences across study designs for these anabolic therapies that will hamper the ability to conduct indirect comparisons/network meta-analyses. In the abaloparatide vs. placebo vs. teriparatide phase 3 trial (NCT01343004), the teriparatide arm was open label and hence subject to bias. Abaloparatide and teriparatide were given for only 18 months, a feature which will likely limit the approval of abaloparatide to 18 months. Yet, teriparatide has been shown to have benefits of ongoing bone formation, increases in BMD, and additional fracture risk reduction during months 18–24 of treatment (Lindsay R, 2016). The open label use of teriparatide in the abaloparatide phase 3 trial and the sub-optimal duration of teriparatide use for only 18 months reduces the probability that the teriparatide data will be deemed appropriate for inclusion in the abaloparatide label. Romosozumab has 2 phase 3 fracture trials; both are markedly different from the Phase 3 study with teriparatide. Specifically, Study NCT01631214 included romosozumab for 12 months followed by open-label alendronate (oral) for at least another 12 months (until end of study) in patients at high risk for fracture. A second phase 3 trial (NCT01575834) involves treatment with romosozumab in lower risk patients for a year followed by denosumab for 24 months (Cosman F NEJM;2016). Teriparatide’s Fracture Prevention Trial was a placebo-controlled trial in patients at high risk for fracture with up to 24 months of observation (Neer R NEJM;2001). Lilly recommends ICER not consider the open label and sub-optimal treatment duration with teriparatide in the abaloparatide phase 3 trial. Instead, Lilly recommends ICER review the fracture and other outcome data from the double-blind, double-dummy, randomized, placebo-controlled Forteo phase 3 fracture trial (Neer R NEJM;2001).

b) Differences in Mechanism of Action (MOA) suggest that comparisons of change in BMD may not reflect change in skeletal health or relative fracture risk reduction. Although measurement of BMD with DXA technology is a methodology available to clinicians to diagnose osteoporosis and monitor treatment, it is well established that there are certain limitations in interpretation of drug treatment based on the MOA of different classes of therapy. It is important to note that DXA measures the mineral content of the bone but does not directly measure bone mass. The mineralization state of the bone thus can influence the interpretation of the results. Antiresorptive therapies inhibit bone remodeling (the removal of old bone and replacement with new bone) and prolong secondary mineralization of existing bone. This increasing accrual of mineral is what is reflected in increasing BMD with this class of therapy. Anabolic therapies add new collagen matrix to the skeleton (new mass) that is subsequently mineralized following the natural biology of bone renewal. The addition of new mass and subsequent mineralization of new collagen matrix is what is reflected in increasing BMD with anabolic therapy (see recent Research Highlight in Nature Reviews Rheumatology in an article entitled “Not all BMD is created Equal”). The manner in which mechanism influences BMD increases is important to recognize, especially when comparing mechanistic differences in three anabolic therapies with clear differences in their action on bone. Teriparatide stimulates robust remodeling in the skeleton across all bone surfaces throughout 24 months of therapy (Dempster D 2016a). Remodeling is a tightly coupled process whereby older, fatigued and highly mineralized bone is removed and is replaced by new bone. In the context of teriparatide therapy, old bone is removed with every cycle and new bone is over replaced – meaning that more bone is added than was present before therapy (Ma YL 2006; Lindsay R 2006). Further, recent data has shown that the new bone that is added to the skeleton with teriparatide has less mineralization density that is more...
heterogeneous –mineral characteristics of younger bone age. Histological confirmation of increased bone mass is important for documenting anabolic effects on the skeleton; Lilly recommends reviewing the following: Jiang Y 2003; Linsday R 2016; Dempster D 2016a, 2016b). Abaloparatide also stimulates remodeling in the skeleton, though to a lesser degree. There is less removal of old bone and less bone formation. Because there is less removal of older, more mineralized bone and some new bone formation, this may be reflected in slightly greater BMD results (~ 1%) than teriparatide at some sites in the H2H trial with these two agents. Lilly recommends ICER consider a recently published paper (Martin and Seeman 2016) which provides important insights into the mechanism of action of abaloparatide. The mechanism whereby romosozumab is anabolic is different than teriparatide and abaloparatide as it stimulates a different mechanism of bone formation referred to as modeling. This process is independent of resorption meaning that new collagen matrix is laid down without removal of any older, more mineralized bone.

Further, data suggest that this drug inhibits bone remodeling while stimulating modeling. Lack of remodeling results in little to no renewal of older bone. BMD increases due to romosozumab are relatively large because older, more highly mineralized bone is not remodeled or removed by this drug, but these large increases do not necessarily reflect improved skeletal health or relatively large reductions in fracture risk relative to teriparatide. Romosozumab is associated with relatively transient increases in bone formation as assessed by increases from baseline in markers of bone formation, including PINP (Cosman F 2016).

e) Lilly recommends that in comparing these different anabolic mechanisms, that the histological documentation of anabolic effect be considered, the duration of anabolic effect, and that recognition of how each unique mechanism contributes to BMD increases be taken into account. Lilly strongly asserts that a BMD comparison is unlikely to represent a true comparison of relative effects of these drugs on bone health or relative fracture risk reduction.

Comparators:
a) The draft scoping document indicates that anabolic agents will be compared to each other and to bisphosphonate (BP) therapy. The document correctly states “…coverage of newer, injectable therapies is highly variable, and may make it more difficult for patients to access treatment.” Real-world place in therapy should be considered for teriparatide (and newer injectable therapies) where substantial access barriers exist in the form of Prior Authorizations (PA) (see references for teriparatide PA’s). In particular, PA criteria usually requires BMD <-3.5 OR BMD<-2.5 AND previous fracture or prior BP use before teriparatide can be utilized.

b) For patients with prior fragility fractures or indicators of higher fracture risk, the AACE guidelines recommend teriparatide, denosumab, or IV zolendronic acid as first line treatments (Camacho 2016).

c) Teriparatide has an excellent, long-term track record on safety and real-world effectiveness in preventing fractures. The substantial body of evidence from real-world prospective and retrospective observational studies should be given strong consideration in terms of effectiveness, safety and other benefits (see Teriparatide Real World Evidence references).

d) Lilly does not recommend comparisons of anabolic therapies to BPs, given the real-world placement of teriparatide and the AACE guidelines for high risk patients. Before considering comparisons of teriparatide to BPs in postmenopausal women, Lilly recommends ICER review several studies which have compared these treatments. (New data from the not yet published VERO study (NCT01709110), the largest and most definitive comparison of teriparatide to BP, can be provided in confidence to ICER upon request. VERO study will be publicly presented at the World Congress of Osteoporosis in March 2017.

Outcomes:
a) Clarification is needed on inclusion of outcomes (i.e., change in BMD, bone turnover). As indicated above, differences in MOA between anabolic treatments suggest that comparison of change in BMD may not accurately or fully reflect change in skeletal health or relative fracture risk reduction. Lilly recommends that ICER consider that teriparatide has much greater increases in bone formation as assessed by PINP than abaloparatide and more durable effects than romosozumab. This indicates more new bone formation during teriparatide treatment. Lilly also recommends considering that teriparatide effects on bone resorption reflect the removal of old, damaged, and fatigued bone, and that the over-replacement with new bone is likely to have a positive effect on bone quality and may help explain the fracture risk reduction observed during teriparatide treatment (Lindsay R 2016).

b) Clarification is needed regarding types of fractures to be assessed. Among the outcomes listed are: hip, clinical vertebral fractures, all fragility fractures, and all fractures; while the model description only mentions hip, vertebral, wrist and tibia. Lilly recommends that ICER consider the endpoints radiographic vertebral fracture and nonvertebral (NV) fracture as the most important osteoporosis fracture endpoints. These are the usual endpoints in osteoporosis clinical trials and in labels in the United States. The importance of morphometric vertebral fractures includes that they are prognostic of future fracture and associated with reduced lung volume, back pain, reduced quality of life, and mortality (Siris ES 2007; Ensrud KE 2000; Krege JH 2015; Lips P 1999; Nevitt MC 1998). For vertebral fracture, the recommended approach is to assess lateral spine radiographs using quantitative morphometry plus semi-quantitative assessment (Prevrhal 2009). For NV fracture, the standard endpoint in most osteoporosis studies has been to exclude fingers, toes, face, skull, and traumatic or pathological fractures (Krege and Wan 2012). For teriparatide effects on hip fracture, Lilly recommends reviewing Eriksen EF 2014; Burge RT 2016.
c) Safety: The frequency of adverse events between teriparatide and abaloparatide should be compared including palpitations, nausea, dizziness, headache, etc. For abaloparatide, several amino acid substitutions of the PTH-rP sequence have been introduced, and the effects of these on immunogenicity should be assessed. Similarly, the immunogenicity of romosozumab should be assessed.

Hypercalcemia: The teriparatide label includes the following information: “FORTEO transiently increased serum calcium, with the maximal effect observed at approximately 4 to 6 hours post-dose. Serum calcium measured at least 16 hours post-dose was not different from pretreatment levels.” Accordingly, recommendations are that serum calcium be measured at least 16 hours after dosing. Because they show pharmacological effect and are probably of little or no clinical significance, Lilly recommends that only calcium assessments obtained 16-24 hours after dosing are relevant.

Risk of osteosarcoma: Teriparatide and abaloparatide have been shown to cause osteosarcoma in rats (see Jolette et al). The amount of safety information regarding this potential issue should be reviewed (see Andrews et al). Note that teriparatide has been used in approximately 2 million patients world-wide with no evidence to date suggesting an effect of teriparatide on osteosarcoma incidence in humans. Given that the incidence of osteosarcoma in humans is 2.5/million/year, very substantial studies and human clinical experience is necessary to assess for potential risk in humans and this risk cannot be assessed through a relatively small clinical trial. Also, the safety experience with teriparatide should not be extended to abaloparatide in light of the 4X higher dosing of abaloparatide (80 mcg/day) versus teriparatide (20 mcg/day) in humans.

Risk of bone overgrowth: Teriparatide has not been shown to result in bone overgrowth during extensive clinical studies and post-marketing surveillance. However, romosozumab is a monoclonal antibody against sclerostin, and people who lack sclerostin have been identified to have bone overgrowth described as sclerosteosis in the more severe form or van Buchem disease in the less severe form (Ref. 269500; Ref. 239100). Accordingly, romosozumab has the theoretical potential to cause bone overgrowth.

Simulation models:

a) Only ER visits and days in the hospital are discussed; however, the cost of fractures includes outpatient costs (e.g., office visits, post-acute care visits, rehabilitation services), as well as acute inpatient care and long-term care. All of these costs are relevant and should be included.

b) There is evidence to support excess mortality from vertebral and non-vertebral fractures (Bliuc D 2013); will this be included in the model’s structure?

c) Teriparatide is limited to 24 months and is usually followed by BP therapy. Therapy offsets following treatment are included in OP cost-effectiveness models. How will the model address these features?

d) Real-world adherence for anabolic therapies should be applied in the model. See Foster S 2011; Langdahl B 2009; Yu S 2012; and Burge RT 2016 for teriparatide adherence in real-world practice. Randomized clinical trials often report non-vertebral composite endpoints with no data for each specific fracture site. Hip fracture is identified as the most important fracture for the evaluation. More information is needed on how the model will handle the NV composite endpoints for the hip fracture evaluation.

We appreciate efforts to create a transparent method for assessing value; however, we feel that consideration should be given to the issues we have raised to ensure a fair and balanced assessment of these treatments. We welcome the opportunity to discuss this in more detail with you if needed.

Sincerely,

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References

**Anabolic Therapies:**

NCT01343004 Study to Evaluate the Safety and Efficacy of BA058 (Abaloparatide) for Prevention of Fracture in Postmenopausal Women.


NCT01575834 Registrational Study With AMG 785 (Romosozumab) to Treat Postmenopausal Osteoporosis


**Clinical Guidelines:**


**Bone Biology and Mechanism of Action:**
"Not all BMD is created equal." Nature Reviews Rheumatology. Published online 17 Mar 2016; doi:10.1038/nrrheum.2016.37


Martin, T. and Seeman, E. (2016), Abaloparatide Is an Anabolic but does it Spare Resorption? J Bone Miner Res. Accepted Author Manuscript. doi:10.1002/jbmr.3042


OTHER:
Bluc D et al; Compound Risk of High Mortality Following Osteoporotic Fracture and Refracture in Elderly Women and Men JBM R 28 (11);2013, pp 2317–2324


Teriparatide Real-World Evidence:
Yu S, Burge RT, Foster S, Gelwicks S, Meadows E, “The Impact of Teriparatide Adherence and Persistence on Fracture Outcomes.” Osteoporosis International 2012;23(3);1102-1113.


Teriparatide Real-World Evidence on Safety:


Prior Authorization Criteria:
United HealthCare 2016
• https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Pharmacy%20Resources/PA_Notification_Forteo_101315PT.pdf

Anthem 2016
The PA criteria below are the same for Anthem’s national or preferred formularies as of 3/15/2016.
https://www11.anthem.com/pharmacyinformation/

Express Scripts 2016
December 22, 2016

Mr. Mitchell Stein, MBA
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Re: Input regarding the Institute for Clinical and Economic Review (ICER) Review of Anabolic Therapies for Osteoporosis: Effectiveness and Value, Background and Scope submitted to publiccomments@icer-review.org.

Dear Mr. Stein:

Radius Health, Inc. is pleased to respond to ICER’s request for information relative to Anabolic Therapies for Osteoporosis: Effectiveness and Value, Background and Scope, December 5, 2016. This letter summarizes the important points discussed on the conference call between ICER and Radius Health on December 12, 2016.

Abaloparatide-SC is an investigational treatment for postmenopausal women with osteoporosis currently under review by the FDA and EMEA and its safety and efficacy have not been established.

We are happy to provide the reference (McCloskey 2016) for the abstract describing the effects of abaloparatide-SC according to baseline fracture probability that we referenced in our last conversation, in addition to the abaloparatide-SC references provided in our December 1, 2016 response.

Radius agrees that a health economics evaluation of osteoporosis must be conducted to address the key drivers of high unmet medical need. Thus, we are providing the following background information regarding osteoporosis to assist in your assessment of the HEOR issues associated with this significant clinical and public health problem. Some of this information has been previously provided to ICER but we felt it would be helpful to emphasize certain points in support of our discussion on December 12, 2016.

Osteoporosis and its associated fractures represent a critical, yet largely overlooked, public health concern in the United States (Office of the Surgeon General 2004). There is consensus among experts that new drugs are urgently required for the debilitating disease of osteoporosis
(Khosla 2016). Bisphosphonates, the most frequently used drugs, can slow the loss of existing bone (i.e., act as antiresorptive agents) but do not build new bone and (as referenced in your scoping document) can be associated with rare (but very serious) adverse events. These issues reduce a patient’s willingness to comply with this form of therapy. Currently teriparatide (recombinant PTH 1-34) is the sole available bone-building (anabolic) treatment on market.

This suboptimal therapeutic environment is partly to blame for the crisis in the diagnosis and treatment of osteoporosis. The reasons for this treatment gap are at least four-fold: at-risk patients are not being screened; those who screen positive are not being accurately diagnosed; high-risk patients are frequently untreated or undertreated; and, when treatment is prescribed, patient non-compliance and non-adherence exists and is well documented (Newman 2011). Thus, emerging therapies are required to fulfill this growing unmet need and minimize the physical, social, and economic burden of osteoporosis.

Radius, therefore, supports ICER’s list of interventions focusing on anabolic agents. Osteoanabolic therapy is often recommended for women at risk of future fracture, including those with recent fracture or multiple fractures (Gelbach 2012). Because those who have experienced a fracture will be at an increased risk of 86% for an additional fracture, they represent a high-risk group likely to benefit from treatment (Kanis 2004). Moreover, in a recent retrospective study, the cost of repeat fractures within the first year was 1.7 to 2.1 times greater than the costs associated with the first fracture (Weaver 2016). Anabolic agents such as parathyroid hormone (PTH) have the potential to both build and maintain bone by improving microarchitecture and thereby increasing the overall bone strength (Meng 1996).

While the spine may be the site in the skeleton (vertebral fractures) most frequently involved in fragility fractures, the majority do not come to clinical attention as they tend to be asymptomatic. Vertebral fractures can, if identified, alert the physician to the presence of osteoporosis and thus prompt therapy; they nonetheless seldom result in the significant morbidity and economic cost more typically associated with nonvertebral fractures (i.e., hip, wrist, and humerus), such as hospitalization, surgery and, with hip fracture, a prolonged convalescence and reduction in health-related quality of life. Nonvertebral fractures have been estimated to account for 73% of the total number of fractures in the United States and 94% of their associated health care costs (Burge 2007). While non-hip, nonvertebral fractures have a lower per-patient cost than hip or vertebral fractures, their total first-year cost is greater because of their higher prevalence (Shi 2009). Notably, distal radius (wrist) fractures are the most common fractures among adults with a peak incidence in white women 45 to 60 years of age (Litwic 1994).

Given the gaps in the therapeutic environment, Radius and others are developing novel anabolic agents that could potentially be used in the treatment of osteoporosis. We, along with clinician-experts, are encouraged by the recent data associated with the anabolic agent that Radius has been developing, abaloparatide-SC. If approved, the investigational drug abaloparatide-SC will be the first anabolic agent to become available since 2002.

A bilateral working group of the American Society of Bone and Mineral Research (ASBMR) and the National Osteoporosis Foundation (NOF), established in 2013, proposed in their assessment that drug therapy for osteoporosis is likely to improve patient outcomes if prescribed per an
individualized “treat-to-goal” paradigm (as opposed to population-oriented, guideline-mandated approaches) (Cummings 2016). Formal or specific recommendations have yet to be made; however, key members of the working group have expressed opinions in the literature in support of initiating, assessing, changing and stopping therapy based on patient-specific clinical data that can, for example, be used to identify a specific pharmacologic regimen that will sufficiently and expeditiously reduce fracture risk. There is an emerging opinion that in some cases a treatment sequence in which an anabolic given first (to build bone rapidly) followed by an antiresorptive (to maintain its integrity) might be preferred (Cosman 2016c). Indeed, recent specialist society guidelines have recommended that teriparatide, denosumab, or zoledronic acid should be considered for patients unable to use oral bisphosphonate therapy and as initial therapy for patients at especially high fracture risk (Camacho 2016).

Sincerely,

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APPENDIX 1: BIBLIOGRAPHY


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December 23, 2016

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To Whom It May Concern:

We write as representatives of the American Association of Clinical Endocrinologists (AACE). AACE is a professional community representing over 7000 endocrinologists worldwide committed to providing the highest quality patient care. We are appreciative of the opportunity to comment on the ICER Draft Scoping document entitled “Anabolic Therapies for Osteoporosis: Effectiveness and Value” dated December 5, 2016.

We appreciate the importance of evidence-based guidance but wish to emphasize the necessity of applying clinical judgment in the care of patients with osteoporosis and encourage ICER to consider this in regard to anabolic therapies for osteoporosis. This is particularly relevant for those individuals with multiple fragility fractures, recent fragility fracture and particularly those at extremely high risk for future fracture, e.g., those with multiple prior fractures, recent prior fracture and a history of falls. Such individuals are at extreme risk for future fracture, are generally not included in the studies comprising the evidence base and are often those for whom endocrinologists commonly recommend anabolic therapy.

Additionally, on our review of the draft document we would like to call the following to your attention:

- There is little acknowledgement of treatment decisions based on fracture risk, as a result, it seems like that those individuals at extremely high risk for recurrent fracture in the short term are unlikely to be viewed differently.
- The osteoporosis community is moving towards emphasis upon maintained independence/quality of life; we encourage this being an important consideration in evaluating the effect of osteoporosis therapies.
- As I mentioned during our call, there are significant costs associated with fractures that may not be accounted for in the current cost estimate of fractures. It is important to account for both direct, and indirect, short term as well as long term costs of these fractures to get a true and useful cost effectiveness analysis.
- The document specifically notes hip, spine and wrist fractures; it is necessary to consider that “major” osteoporosis-related fractures constitute only approximately 50% of the total fragility fracture burden.
- To our knowledge, there are no studies directly comparing abaloparatide and romosozumab making comparison of efficacy challenging.
- The stated plan to report absolute risk reduction and number needed to treat would seem to be related to baseline fracture risk.

The Voice of Clinical Endocrinology
The current evidence base for anabolic agents will not be able to account for a lot of real world scenarios that clinicians face. An example would be patients who are failing or are unable to tolerate antiresorptive agents and only do well on anabolic therapy. Such patients who had prior treatment are often excluded from clinical trials and their outcomes will not be available for analysis.

Finally, it is important to note that anabolic agents play a very important role in osteoporosis management. The project that is being undertaken must not decrease, but rather should increase access to these agents. We appreciate the opportunity to comment on this very important project.

Sincerely,

Pauline M. Camacho, MD, FACE
President; Chair, Bone & Parathyroid Scientific Committee

PC/sml
December 23, 2016

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Public Comments - ICER Osteoporosis Draft Scoping Document

Dear Dr. Pearson,

On behalf of the National Bone Health Alliance (NBHA, www.nbha.org), we are pleased to provide comments on the Institute for Clinical and Economic Review (ICER) Anabolic Therapies for Osteoporosis: Effectiveness and Value Draft Background and Scope released on December 5, 2016. The NBHA is a public-private partnership on bone health that brings together the expertise and resources of its 51 non-profit and private sector member organizations as well as liaisons from 5 federal government agencies (CDC, CMS, FDA, NASA and NIH) to improve the overall health and quality of life of all Americans by enhancing their bone health.

We would like to thank ICER for its direct engagement with NBHA, including multiple phone calls with NBHA staff and leadership, and are pleased to organize a working group of leading clinical and academic bone health experts to interface with ICER directly as the development of the osteoporosis report continues as well as provide our written feedback.

Osteoporosis is a prevalent disease characterized by weakened and fragile bone tissue, leading to an increased chance of fracture; as of 2010, over 10 million Americans age 50 and above have osteoporosis and an additional 43 million Americans have low bone mass, placing them at increased risk of suffering from a fracture caused by osteoporosis. It is projected that by the year 2030, 13 million Americans will have osteoporosis and an additional 57 million will have low bone mass. Therefore, it is important patients suffering from devastating fractures as a result of osteoporosis have access to all possible interventions to reduce future fracture risk.

Overall, many individuals with or at risk for osteoporosis do not receive appropriate testing to diagnose possible osteoporosis, even after a fracture. And once they are diagnosed (by testing or by the occurrence of a fracture), many patients are still not being prescribed effective anti-osteoporosis therapies. Of women age 65 to 85 with an osteoporosis-related fracture, only 30 percent had either a bone mineral density test or were prescribed a medication to treat or prevent osteoporosis in the six months after the fracture.
The most devastating (and costly) fracture is a hip fracture, with up to 25 percent of hip fracture patients dying within a year\[^{iv}\]. Alarming new Medicare data shows that, after more than a 30-year downward trend in the incidence of hip fractures in the U.S., a plateau has emerged in the last few years.\[^{iv}\]

Please find below the following comments on the *Effectiveness and Value Draft Background and Scope*, understanding that the details of the final scope of this report will be refined further:

- Please clarify why only direct health care costs are included, as the full economic impact of fractures caused by osteoporosis includes not only direct health care costs but also indirect, societal costs such as caregiver burden and lost income for patients. Additionally, forearm fractures, which occur in younger age and also incur income loss due to sick leave, should be included as an outcome.

- Related to the point above, depending on the structure of the caretaker system, much of the burden to society of a fracture may be in the municipalities (e.g., skilled nursing, rehabilitation and nursing home-related costs that in some cases exceed the direct costs related to the initial care for the fracture). Further, please note that the cost of first and second fracture events differ\[^{v}\].

- How will the proposed method be applied to identify resource consumption and unit prices for the health care costs considered though relevant available published literature? If the analyses are limited to this data source, the end results may be significantly different from what would be observed in a real-world setting.

- Which method(s) will ICER use to conduct the health economic assessment? It appears (though is not directly stated) that Markov models for transition between health states will be applied.

- How will the models incorporate cost effectiveness as well as cost utility (as the only QALYs mentioned in the draft scope is cost utility)? Which models are going to be compared?

- Please clarify which quality of life weights will be used such as EQ-5D or mean-time trade off (TTO), as values can vary markedly based on the method used and whether they were hypothetical or experienced.

- It is stated that the authors will use randomized controlled trials as well as high-quality systematic reviews (high-quality comparative cohort studies will be considered); given that only teriparatide would have any relevant observational studies available, it may not be appropriate to use these studies.

- The simulation models that focus on comparative value are interesting and important, but given there may be many unknown factors (and assumptions) potentially made in these models, particularly for the newer agents, how will this limitation be acknowledged? Are there any plans to address this, such as sensitivity analyses?

Additionally, see below some specific content inputs:

- **Page 1 (“Background”):**
  - As currently written, the background does not adequately address the need for comparative value studies with anabolic agents.
The first sentence of the third paragraph, “Osteoporotic fractures can cause a pronounced curving of the spine (kyphosis), the loss of height, and rib fractures can make breathing difficult”, appears out of place.

It is stated that first-line therapy is oral bisphosphonates, which should be qualified to indicate that bisphosphonates are considered “first-line therapy for many patients” (as there are some patients in which other agents may be considered first line therapy, such as those with very low vertebral bone density or on chronic high doses of glucocorticoids).

Page 3 (“Figure 1. Analytic Framework: Anabolic Therapies for Osteoporosis”): The figure does not suggest that the health utilization outcomes and patient-centered outcomes related to harms will be evaluated, but only treatment efficacy.

Page 4 (“Key Harms”): Add hypercalcemia to list of key harms.

Page 5: It appears that the simulation models will use time-dependent variables and assess and compare outcomes while a patient is on or off treatment; given that the effects of bisphosphonates may persist for years after discontinuation of therapy, strict assessment of time-varying effects are difficult to ascertain.

As ICER continues to refine and develop this osteoporosis report, we strongly encourage you to continue to engage with us as well as individual patients and patient societies to ensure their feedback is taken into account. Given the significant care gaps we have identified, it is critical that policy and communication recommendations stemming from this report reflect and identify potential remedies for these challenges.

We thank you for your consideration of this input and look forward to our working group providing further oral feedback as you refine the scope of this effort. If you have any questions about these comments or would like additional information about the NBHA, please do not hesitate to contact David Lee, MPA, NBHA Executive Director, at david.lee@nbha.org or (703) 647-3003. Thank you.

Sincerely,

Robert Adler, MD  
Co-Chair, National Bone Health Alliance and Professor of Internal Medicine, Epidemiology and Community Health, Virginia Commonwealth University School of Medicine and Chief, Endocrinology and Metabolism, McGuire Veterans Affairs Medical Center, Richmond, VA

Kenneth Saag, MD, MSc  
Co-Chair, National Bone Health Alliance and Jane Knight Lowe Professor of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham (UAB) and Professor of Epidemiology, UAB School of Public Health, Birmingham, AL

cc: David Lee, MPA, Executive Director, National Bone Health Alliance


December 23, 2016

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA  02109

Re: Public Comments - ICER Osteoporosis Draft Scoping Document

Dear Dr. Pearson,

On behalf of the National Osteoporosis Foundation (NOF, www.nof.org), I am writing to provide input on the Institute for Clinical and Economic Review (ICER) Anabolic Therapies for Osteoporosis: Effectiveness and Value Draft Background and Scope released on December 5, 2016. The National Osteoporosis Foundation (NOF) is the leading patient and healthcare professional non-profit, voluntary health organization solely dedicated to making bone health a reality and lifelong priority for all individuals. NOF achieves its mission through programs of awareness and prevention, advocacy, public and health professional education and research.

NOF is committed to increasing the patient’s understanding of his/her risk for – as well as the serious consequences of – osteoporosis; and encouraging patients and physicians to embrace action steps associated with prevention, diagnosis and treatment.

I appreciate the strong engagement of ICER with us as you develop this report into 2017, and would like to express our willingness to continue to interact with you (as well as identify individual patients should you wish to have direct conversations with some of the osteoporosis patients we work with closely).

I am writing to you on behalf of the 53 million Americans age 50 and above at risk to suffer from a fracture caused by osteoporosis (over 10 million Americans with osteoporosis and an additional 43 million with low bone mass, placing them at increased risk of suffering from a fracture caused by osteoporosis).
To provide some insights from our community of osteoporosis patients (as well as caregivers directly impacted by this disease), I would like to share some of the results of a 80-question patient and caregiver Bone Health Index Survey disseminated to NOF’s approximately 28,000 online community members earlier this yearii. Patients ranked loss of independence (42%) and lost mobility (25%) as their leading concerns about aging and osteoporosis patients and caregivers of osteoporosis patients noted they were most concerned that they would be unable to manage their patient or loved one’s care (50%).

Among the additional survey findings:

- **52% of the patients who responded to the survey said they had broken a bone**, with the average number of bones broken being 3; yet, surprisingly, **44% said they were only somewhat or not concerned about fracturing again**
- **60% of those who said they had broke a bone were not referred for a bone density test after the fracture to determine if osteoporosis was the underlying cause of the fracture**
- **Less than half (47%) were prescribed an osteoporosis medication for treatment**
- **Of the patients who were on osteoporosis treatment, 92% said they had read or viewed negative information about the medication**
  - Their length of time on medication was short, with 42% saying they’d been on treatment for less than two years
- **38% said they were prescribed an osteoporosis medication they didn’t take**
  - Fear of side effects from the medication was the leading factor for not taking the medication (79%)
- **51% of patients who were on a medication said they stopped taking the osteoporosis medication most commonly because of the side effects they experienced (53%) or out of concern for the risk of side effects (38%)**
- **89% knew that proper diet and exercise, including getting the recommended daily allowance of calcium and vitamin D, is an important part of treating osteoporosis**
- **90% knew that osteoporosis cannot be treated solely through diet and exercise**

These survey findings are striking, particularly considering the large number of respondents who had broken a bone (with the average number being three) but were not particularly concerned about fracturing again and points out many of the challenges to getting patients diagnosed, screened and treated for the disease, despite the high prevalence of the disease in the age 50 and above population (which will continue to rise as the American population continues to age).

I urge you to keep these survey results in mind as you proceed to define the scope of this review and draft the evidence report and we look forward to help facilitate direct engagement with individual patients to ensure they are kept at the center of your model.

On behalf of National Osteoporosis Foundation, thank you for your consideration of this input and do not hesitate to contact me directly at 703-647-3020 or amy.porter@nof.org with any questions or additional input you require.
Sincerely,

Amy Porter  
Executive Director and CEO  
National Osteoporosis Foundation

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Osteoporosis International

Response to ICER: Anabolic Therapies
December 23, 2016

To Whom It May Concern,

“Longevity is increasing the burden of fractures. Although antiresorptive therapy slows remodeling, it does not prevent or repair microstructural deterioration. The challenge is to reconstruct the skeleton. The more advanced the patient’s age, the more likely that microstructural deterioration is severe and more rational the choice of an anabolic agent as first-line therapy.”1

Anabolic therapies are distinct from antiresorptive therapies in their ability to augment bone density to a greater extent, rebuild bone microstructure and further enhance bone strength. The efficacy of antiresorptive drugs is limited by the fact that in addition to inhibiting resorption, within a few months of administration they also inhibit bone formation and the more potent the antiresorptive effect, the more potent is the anti-formative effect. Anabolic drugs, on the other hand, stimulate bone formation. Teriparatide and abaloparatide also stimulate resorption but to a lesser extent than they stimulate formation, whereas romosozumab stimulates formation and inhibits resorption.

Although there are few head to head trials that have been or will ever be done to compare fracture outcomes directly between anabolic and antiresorptive treatment, the few available head to head studies indicate superior benefit at least for vertebral fracture between teriparatide and alendronate in patients on glucocorticoid therapy2,3 and between teriparatide and risedronate in patients with acute vertebral fracture.4 In the glucocorticoid study, vertebral fractures were 90% less common with teriparatide than with alendronate and in the acute vertebral fracture study, vertebral fractures were 50% less common with teriparatide than with risedronate. It is well accepted that morphometric vertebral fractures are as important an outcome as are acute clinically symptomatic vertebral fractures in terms of their ultimate impact on health outcomes, morbidity and mortality5, consistent with all of the FDA-regulated pivotal trial outcomes for pharmacologic treatment of osteoporosis. Studies that compare the most important surrogate for fracture (bone strength via finite element modeling of CT data) also indicate that teriparatide is superior to alendronate.6,7 These findings are in fact consistent with the greater improvement in BMD (at least at the spine) in trials comparing teriparatide with bisphosphonates.8 Most importantly, the common mechanisms by which anabolic therapies work (increased number, lifespan, and activity of osteoblasts) is consistent with a fundamental increase in bone tissue that has the capability of reversing the structural defects that cause skeletal fragility.

Teriparatide shows an early antifracture effect for both vertebral and nonvertebral fracture (within 18 months). The two new anabolic therapies show substantial antifracture efficacy within 18 months in the case of abaloparatide (both vertebral and nonvertebral9), and within 1 year in the case of romosozumab (both vertebral, all clinical fractures and nonvertebral for most geographic regions10). Early fracture efficacy is
critical in patients at high imminent risk for fracture. Most patients who have had recent fractures are at very high imminent risk over 1-2 years after the first fracture.\textsuperscript{11,12}

Not only are patients with a high imminent risk for fracture good candidates for anabolic treatment, patients with very high long-term risk of fracture due to very low BMD at an early age are also good candidates for anabolic therapy. In this latter case, imminent risk may not be very high, but long-term risk is very high. For example a relatively young woman (age 55), beginning with a BMD T-Score below -3, will not (on average) achieve a T-Score above the osteoporosis range with a 3-5 year course of bisphosphonate treatment. However, a treatment sequence of potent anabolic treatment for 1-2 years followed by an antiresorptive agent for 3-4 years will likely produce a BMD T-Score above the osteoporotic range. It is critical to note that at least for the hip region, the impact of anabolic followed by antiresorptive therapy on BMD is much greater than the sequence of antiresorptive followed by anabolic therapy. Moreover, BMD will increase much faster and will attain a greater level if treatment is initiated with anabolic therapy.\textsuperscript{10,13,14} Treatment sequence is important, particularly for the hip region.\textsuperscript{15}

There is a ceiling with most antiresorptive therapies in terms of efficacy. Certainly with bisphosphonates, BMD plateaus after about 3 years and prolonged antifracture efficacy beyond 3-4 years is difficult to demonstrate. At the same time, rare adverse effects of ONJ and AFF are related to duration of antiresorptive treatment. Moreover, we know that BMD is an excellent surrogate for fracture risk both in patients who are not yet treated, as well as those who have already received osteoporosis treatment. BMD after 5 years of treatment with alendronate\textsuperscript{16}, after 3 years of treatment with intravenous zoledronic acid\textsuperscript{17}, and at any time point after treatment with denosumab\textsuperscript{18}, is a predictor of subsequent fracture risk. Therefore, even if an initial course of antiresorptive treatment will provide a relative reduction in risk of fracture, patients who start at very high risk will still remain at high absolute risk of fracture 3 years later. The practice of transitioning patients to an anabolic treatment at that point has less evidence of efficacy and certainly does not produce as substantial an impact on BMD, particularly in the hip region, as does treatment beginning with an anabolic agent.

Osteoporosis is characterized by reduced bone density and microarchitectural deterioration leading to increased fracture risk. While paired bone biopsy studies have shown that antiresorptive drugs are able to prevent further deterioration in bone structure\textsuperscript{19}, only anabolic drugs agents have been shown to restore microstructure towards normal in both cortical and cancellous skeletal compartments.\textsuperscript{20,21} In other words, only anabolic drugs have the potential to reverse the disease process, rather than simply prevent it from worsening. Therefore, in patients with more severe osteoporosis (by BMD and/or fracture criteria), it is clear that the best approach is to restore microstructural integrity with a short course (1-2 years) of an anabolic agent and then maintain the improved bone structure with an antiresorptive agent.

For both patients at high imminent risk of fracture as well as those at high long-term risk of fracture, early efficacy and greater efficacy can be achieved beginning with anabolic treatment. The ultimate impact is that fracture risk and BMD Goals can be achieved with
with fewer years of treatment. The majority of thought leaders in the osteoporosis field would agree with this as an advantage over prolonged antiresorptive therapy alone.

References
11. Balasubramanian A, Zhang J, Chen L, et al. High Risk of Second Fracture Within 1, 2, 5 Years After Prior Fracture Among Women 65 Years or Older. *ASBMR; 2016; Atlanta, GA.*
treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: Results of the ACTIVExtend trial. Mayo Clin Proc, In Press


Dr. Felicia Cosman
Professor of Medicine at Columbia University College of Physicians and Surgeons
Osteoporosis Specialist/Endocrinologist Helen Hayes Hospital
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Dr. David W. Dempster
Professor of Clinical Pathology and Cell Biology at Columbia University College of Physicians and Surgeons Senior Research Scientist, Helen Hayes Hospital
Associate Editor, Osteoporosis International
Dear Dr. Pearson:

On behalf of United Rheumatology (UR), I am pleased to respond to the Draft Background and Scope Document for *Anabolic Therapies for Osteoporosis: Effectiveness and Value*. UR supports practicing, independent rheumatologists in their mission to strengthen the doctor-patient relationship and support patient-centered, high quality, cost-effective care. Our rapidly growing network is comprised of 295 physician members within 115 practices across 29 states.

While we support ICER’s decision to evaluate therapies for osteoporosis, there are a number of amendments required in order to accurately represent and review treatment of the disease.

**General Comments**

ICER’s review should not be limited to current and proposed anabolic agents. Given the considerations listed below, we propose that all parenteral drugs, including denosumab and zoledronate, be included.

- **Use of the Term Anabolic** - Of the drugs ICER has proposed to include, only two are pure anabolic drugs (teriparatide/Forteo and abaloparatide); romosozumab is a drug with both anabolic and anti-resorptive properties.
- **FDA Approval** - Of the three drugs proposed, just one, teriparatide, has been approved by the FDA. Including currently utilized drugs is critical to accurate modeling and to producing an actionable report that will solicit real world feedback from patients and practitioners alike.
- **Treatment Duration** - Treatment with teriparatide is limited to 2 years due to the potential development of osteosarcoma with longer durations of therapy, and it is expected that abaloparatide will have a similar treatment limit. It is anticipated that romosozumab will be restricted to 12 months of treatment based on the findings of a pivotal phase three trial. The 1-2 year treatment duration across all three drugs will inhibit ICER’s ability to “assess the lifetime cost-effectiveness of treatment” and “explore the potential health system budgetary impact of treatment over a five-year horizon,” as proposed.
- **Pre- and Post-anabolic therapy (sequential treatment)** - Increases in bone mineral density (BMD) imparted by anabolic drugs are lost over 1-2 years if not followed by an appropriate anti-resorptive drug. As such, it is not possible to accurately model the long-term impact of these therapies without examining the drugs subsequently required in treatment, such as denosumab and zoledronate. Additionally, recent studies suggest that if potent antiresorptive drugs such as bisphosphonates or denosumab are used prior to treatment with anabolic drugs such as teriparatide, abaloparatide, or romosozumab they may partially inhibit their bone building properties especially in the hip. Given sequential therapy could have a significant impact on fracture prevention and the validity of any proposed simulation models focused on comparative value, anabolic drugs should not be studied in isolation.
• **Value of treatment** - Recently released Medicare drug spend data reflects a number of key considerations for the cost, and coverage of, osteoporosis drugs. For example, the 2015 CMS data reflects significantly higher spending (over $1B) on denosumab, a drug that ICER has opted to not study, than teriparatide (over $430M). The significantly lower CMS expense for teriparatide in part reflects the drug’s availability only through Medicare Part D whereas denosumab is available through both Part B and Part D. As a consequence, many patients who should be treated with teriparatide are unable to afford the drug due to limited Part D coverage unless they have also purchased a supplemental drug benefit plan. In assessing the value of treatment, the price of the drug – as well as the real-world practicality of the patient’s access to treatment – must be considered.

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**Background**

*We encourage ICER to consider revising the following elements in characterizing osteoporosis:*

• **Definition of Osteoporosis** - We recommend using the NIH Consensus definition, which defines osteoporosis as “a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality...Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures) and mineralization” and “acknowledges[s] a common misperception that osteoporosis is always the result of bone loss. Bone loss commonly occurs as men and women age; however, an individual who does not reach optimal (i.e., peak) bone mass during childhood and adolescence may develop osteoporosis without the occurrence of accelerated bone loss. Hence sub-optimal bone growth in childhood and adolescence is as important as bone loss to the development of osteoporosis.”

• **Prevalence** - The “approximately 10 million Americans” referenced is an underestimation that relies on the densitometric definition of osteoporosis. The number of individuals at risk for fracture is far greater, and many people with low bone mass/osteopenia have already had or are at increased risk for fracture (based on FRAX), which warrants drug therapy. It should be noted that approximately 52 million people in the U.S. are affected by osteoporosis or low bone mass.

• **First Line Therapy** - ICER’s summary inaccurately implies that all patients should begin on an oral bisphosphonate (BP) and, failing that, switch to an iv BP. (1) *An oral BP is not appropriate for patients with significant GERD, esophageal motility disorders, or renal insufficiency (estimated GFR of 35 or lower).* The iv BP zoledronate is appropriate for patients with significant GERD or other gastric/esophageal diseases; however, iv BPs are also contraindicated in those with renal insufficiency. (2) *An oral BP is not the best treatment for patients at high risk for fracture (based on multiple prior fractures and/or a T-score below -3.0).* For example, patients who are found to have several grade 2 or grade 3 vertebral body compression fractures are at far greater risk than those with a single grade 1 fracture, and may require treatment with teriparatide or denosumab though in the future abaloparatide or romosozumab may also be options. The FDA appropriately recognizes the non-uniform risk for future fractures; the labeling of osteoporotic drug therapy currently reserves the indication “high risk for fracture” for teriparatide and denosumab. (3) *It should be recognized that generic oral BPs are now almost exclusively used instead of brand name BPs due to their significantly lower cost, despite the fact that clinical fracture data was derived from brand name BPs.* Recent studies demonstrate significant variability in disintegration...
and absorption rates among individual generic BPs which can affect tolerability, adherence, and possibly efficacy when compared to brand-name equivalents.

### Populations

**We encourage ICER to also study osteoporosis in males and those on glucocorticoids for the reasons outlined below.**

- One in four men have an osteoporotic fracture in their lifetime, with direct medical costs in 2010 estimated to be more than $4.5 billion in the U.S.; moreover, mortality associated with fractures is significantly higher in men than women. Among the drugs given parenterally, teriparatide, denosumab, and zoledronate are all approved for male osteoporosis.
- Glucocorticoid induced osteoporosis (GIO) is a common but preventable side effect of steroid use. Incidence of new fractures is estimated to be as high as 17% after 1 year of therapy and fractures can occur in 30-50% of those treated chronically. Teriparatide and zoledronate – but not denosumab – are approved for treatment of GIO.

### Interventions and Comparators

ICER’s intention “to compare all the (studied/anabolic) agents to each and to bisphosphonate therapy,” conflicts with the omission of denosumab as both an intervention and comparator.

### Outcomes

**We encourage ICER to consider the following edits to the Outcomes section on Page 4:**

- **Surrogate Outcomes** - Morphometric/radiographic vertebral fractures, which are often measured in clinical trials as either a primary or secondary outcome and can be compared across drug therapies, are not a surrogate outcome and represent the same risk for future fracture as clinical vertebral fractures. These should be included under “all fragility fractures” within “Outcomes”.
- **Key Harms** - Hypercalcemia, not hypocalcemia, should be listed if only anabolic drugs are to be studied. Hypocalcemia is a possible side effect of potent antiresorptives such as denosumab or zoledronate. Additionally, drug addiction as a result of chronic pain associated with fractures should be included.

**We recommend the following edit to Figure 1 (Analytic Framework):**

- **Health Care Utilization Outcomes** - Fracture repair, including total hip arthroplasty, ORIF, and vertebral augmentation (kyphoplasty and vertebroplasty) should be added.

### Settings

- The substantial costs of inpatient care for fracture repair, including long-term care and rehabilitation, should be considered.

### Simulation Models Focusing on Comparative Value

The Opening Statement, “injectable medications are relatively expensive compared to oral…” further underscores the need to include all parenteral drugs used to treat osteoporosis including teriparatide, denosumab, zoledronate, and future drugs abaloparatide and romosozumab.

Sincerely,

Max Hamburger, MD FACP FACR
President, United Rheumatology