

**Amgen’s Response to the Institute for Clinical and Economic Review (ICER)
Draft Report on Anabolic Therapies for Osteoporosis in Postmenopausal Women:
Effectiveness and Value**

Amgen appreciates the opportunity to comment on the ICER draft report “Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value.” Osteoporosis is an important disease that remains under-diagnosed and under-treated, and in which innovative therapies have an important impact on patients. Hence, it is critical that any assessment on this topic keeps patients at the center and uses appropriate methods and inputs.

Before sharing our comments on ICER’s draft report, we would like to acknowledge that Amgen no longer expects FDA approval of EVENITY (romosozumab) in 2017. Amgen and UCB recently announced that the romosozumab ARCH study met both primary endpoints and the key secondary endpoint. In ARCH, treatment with EVENITY for 12 months was followed by alendronate for at least 12 months. At 24 months, women in the EVENITY treatment group experienced statistically significant risk reductions of 50% in new vertebral fractures, 19% in non-vertebral fractures and 27% in clinical fractures, in addition to nominally significant reduction in hip fractures compared to alendronate alone. Overall, adverse events and serious adverse events were generally similar between treatment groups throughout the study. An imbalance in positively adjudicated cardiovascular serious adverse events was observed as a new safety signal (2.5 percent EVENITY versus 1.9 percent alendronate at 12 months). (Appendix A). Amgen has agreed with the FDA that the ARCH data should be considered in the regulatory review prior to the initial marketing authorization. It is important that the regulatory agencies review the full evidence package of FRAME and ARCH before a value assessment is conducted. Amgen asks ICER to remove romosozumab completely from this assessment as we believe reaching conclusions around the value of new technologies based on incomplete information is contrary to basic medical research principles and can have unintended negative consequences for patients.

While we expect ICER to remove romosozumab, we have provided our comments on the draft report to help correct some of its major issues and deficiencies.

ICER’s osteoporosis assessment has serious methodological flaws that compromise its results, which inappropriately imply overall poor value of bone-forming agents. For example, ICER selected an inappropriate comparator for this assessment despite extensive feedback on this issue. ICER’s comparative clinical effectiveness is based on a literature review that does not include one of the comparators, zoledronic acid (ZA), in the search strategy (draft report tables A2-A4). Moreover, ICER’s base case cost-effectiveness model utilizes clinically unsound efficacy assumptions and data inputs, and does not reflect the uncertainty associated with efficacy estimates and their impact on the results and conclusions. Summarized below are the critical issues and recommendations, and how to address them based on an understanding of economic evaluation; clinical practice; the biology of osteoporosis; and of patients suffering its consequences.

Critical issues and recommendations:

1. **Comparing bone-forming agents to bisphosphonates is an inappropriate way to estimate the value of *bone-forming agents*.** Despite early feedback from multiple stakeholders, ICER continues to base their value assessment of bone-forming agents (teriparatide, abaloparatide, and romosozumab) on a comparison to a bisphosphonate. ICER selected ZA as the comparator, with the rationale that this agent is used in patients at high risk for fracture. However, this comparison is fraught with limitations. Bisphosphonates, including ZA, are a different class of agents that slow bone loss rather than building new bone, and are generally used in a treatment context that differs

from bone-forming agents. **Recommendation:** Value assessments should compare newer therapies to the most relevant comparator being used in the same context, with the same therapeutic objective in the same population. In this case, a comparison across bone-forming agents would be most appropriate.

2. **ICER's assessment is based on clinically unfounded efficacy assumptions.** (1). Available hip fracture data (e.g., romosozumab's HR 0.54 vs. placebo at 12 months) are not used for any product due to some not having appropriate data (i.e., abaloparatide) and non-vertebral fracture data are used to model hip fractures for all products (2). Time-dependent treatment effects are not considered despite existing evidence of the rapid onset of bone-forming agents (1-2 years), particularly romosozumab (1 year), in contrast to 3-5 years of ZA and bisphosphonates in general. **Recommendation:** (1). ICER should use existing hip fracture data and replace with non-vertebral fracture data only for those treatments lacking robust data (e.g., abaloparatide), (2). ICER should incorporate time-dependent efficacy data into the model to capture the rapid effect of bone-forming agents, particularly romosozumab.
3. **ICER underestimates fracture costs and overall disease burden, including mortality.** (1). Short and long-term fracture costs (the primary direct medical cost) are underestimated by ICER by using cost data from as far back as 2001 and 1989 respectively, (2). Fracture-related impact on death is inadequately captured. **Recommendation:** ICER should use up-to-date short and long-term cost estimates for fractures based on a systematic review of the literature. ICER should also account for the downstream disease burden of fractures in terms of their impact on mortality as inputs into their model, to better capture the value of preventing such catastrophic events for patients.
4. **ICER uses unrealistic base case assumptions that do not reflect clinical practice.** (1). ICER assumes 100% persistence for ZA despite their acknowledgment of real world evidence indicating that up to 60% of US patients discontinue ZA after 1 injection. (2). The assumption of a rate of decline of the effect over 10-years post-ZA appears unsubstantiated as it is based on data on residual effects on the bone and not on long-term fracture protection data over 10 years. **Recommendation:** ICER should simulate real world estimates of persistence of each therapy over time and assume credible ranges for the decline of effect over time.
5. **ICER's model is unstable as demonstrated by the extremely large volatility of its results.** In ICER's model, variation in one model input changes the results by millions of dollars per QALY. This is a sign of enormous uncertainty and lack of robustness of the model. However, ICER chose to focus the sensitivity analysis on factors with little impact on results such as utility (40% of ICER's one-way sensitivity analysis) and reaches strong and definitive conclusions that seem disconnected from the underlying uncertainty. **Recommendation:** ICER should choose clinically sound base case assumptions and conduct a robust assessment of uncertainty around data inputs and assumptions, and utilize the results to appropriately inform conclusions of the assessment as per established good practice in economic evaluation.¹

The above-mentioned issues are further detailed below:

1. Comparing bone-forming agents to bisphosphonates is an inappropriate way to estimate the value of bone-forming agents.

Bone-forming agents are viewed as a distinct class of therapy by the medical community.²⁻⁴ Although ICER correctly notes treatment recommendations of a T-score ≤ -2.5 or 10-year fracture risk based on FRAX (hip fracture risk of $\geq 3\%$ or major osteoporosis-related fracture risk of $\geq 20\%$), patients who

receive the bone-forming agent, teriparatide, tend to be at a much higher fracture risk relative to patients treated with antiresorptive agents.^{5,6} Real world evidence show that patients receiving teriparatide were significantly older, had more comorbidities and fracture-related hospitalizations and substantially higher baseline fracture rates.⁷⁻⁹ In these higher-risk patients, bone-forming agents can improve impaired bone mass and structure allowing for more rapid offset of fracture risk. Subsequent sequencing to antiresorptive agents may 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. Amgen is conducting research that will further identify patients who are at high risk of a near-term fracture and can provide additional information on this.

ICER compares bone-forming agents to a bisphosphonate requiring making a comparison across different classes of agents, generally used in different treatment contexts, in different patients and over different timeframes. This indicates a lack of recognition of patients' heterogeneity in their needs and preferences and it seems more a misleading price-centric comparison than one informing a relevant decision. Furthermore, ICER also compares active treatments to *no treatment*, which again represents an unrealistic scenario where bone-forming agents may be considered and yet does not compare bone-forming agents to each other, which would be a more useful exercise of value assessment.

Value assessments should compare therapies intended for use in a given population with the same therapeutic needs. In this case, a comparison across bone-forming agents would be most appropriate.

2. ICER's assessment is based on clinically unfounded efficacy assumptions.

Product-Specific Hip Fracture Estimates

The ICER base case model uses nonvertebral fracture estimates in place of hip fracture estimates for all products evaluated. This could be considered appropriate in the case of abaloparatide since hip fracture estimates could not be accurately calculated given only two hip fractures were observed (both in the placebo arm) in the ACTIVE trial¹⁰. However, using nonvertebral data instead of hip fracture data for romosozumab is inappropriate as hip fractures are reported from the FRAME study: HR 0.54 (0.22 – 1.35) for romosozumab vs. placebo at 12 months and 0.50 (0.24 – 1.04) for romosozumab/denosumab vs. placebo/denosumab at 24 months.¹¹

ICER only tests this flawed assumption in a sensitivity analysis resulting in almost double the estimated health benefit and a change in result for romosozumab from over \$4 million dollars per QALY to less than \$193,000 per QALY (draft report tables 16 and 24).

Time-Dependent Efficacy

ICER assumes an immediate, full effect of ZA, which over-estimates the value of ZA. Clinical trials have reported effects at time points that are not always aligned with each other; while cross-study comparisons require considering heterogeneity in patient populations studied, the time frame of efficacy assessments across studies should be reflected in ICER's modeling. The clinical trial data ICER is considering, in combination with an understanding of the mechanism of action of each therapy, strongly suggest a faster effect attributable to bone-forming agents (1-2 years) and romosozumab in particular (1 year) in contrast with a slower, more gradual effect with bisphosphonates such as ZA, particularly for non-vertebral fracture.¹⁰⁻¹³

It is also important to note that romosozumab is penalized in the ICER assessment for offering a 1 year treatment option, with rapid results (at 1 year), since it results in only 7 years of treatment for the sequence including romosozumab compared to 8 years for the sequences including teriparatide or

abaloparatide (2 years treatment). This stems from the questionable assumption of a fixed 6 year sequenced treatment with ZA following each bone-forming agent, instead of a non-sequenced comparison or the use of the same total time frame across products (i.e. all treatment sequenced for X years).

ICER should use all relevant data available for each product and their specific time-dependent benefits without imposing artificially created rules that penalize specific products unnecessarily.

3. ICER underestimates fracture costs and overall disease burden, including mortality.

ICER's model utilizes fracture and post fracture cost inputs from as far back as 2001 and 1989 respectively, with just an adjustment for inflation that could not possibly account for the changes in care and the use of new technology that has occurred in the last 25 years. This represents a gross underestimation of the financial burden of osteoporosis even when compared to estimates from 2007¹⁴ with differences of up to \$10,000 dollars per fracture, or about 50% of their cost, observed.

An equally concerning issue identified in ICER's assessment is their reference of Tosteson et al 2007 in the claim that "excess mortality only occurred after hip fractures." Tosteson does not make that claim.¹⁵ The article focuses on mortality associated with hip fractures, and states that vertebral and nonvertebral fractures were too difficult to identify from retrospective patient charts and were thus not considered. In a literature search, we identified multiple references providing evidence that mortality increases after other fracture types such as vertebral fracture.¹⁶⁻²³

Underestimating the burden of osteoporosis does a disservice to patients and physicians by undervaluing the impact of fracture-related mortality and costs, and ultimately the value of the bone-forming agents that have demonstrated their efficacy in preventing fractures. The incomplete picture painted by ICER could perpetuate under treatment of an already undertreated patient group and disease in general with often quoted treatment rates of 20% or less^{24,25} even in high risk elderly post-fracture patients.

ICER should use up-to-date short and long-term cost estimates for fractures based on systematic literature review and appropriately account for the downstream disease burden of fractures in terms of their impact on mortality, as inputs into their model to better capture the value of preventing such catastrophic events for patients.

4. ICER uses unrealistic base case assumptions that do not reflect clinical practice.

ICER assumes 100% persistence for ZA.; however, recent peer-reviewed publications^{26,27} on real world use of osteoporosis therapies indicate 30-60% of US patients discontinue ZA after 1 injection. ICER's report acknowledges the issue citing a 59% discontinuation of ZA by two years and 67% for teriparatide, and yet assumes 100% persistence, for six years in the case of ZA. Importantly, compromised persistence for ZA may be related to the high incidence of infusion reactions that occur with ZA.¹⁰⁻¹³ In addition, the assumption of an additional 10-years offset of effect for ZA is based on bone mineral density data of much shorter duration, which show only residual bone mineral density effects on the bone (not long-term fracture protection over 10 years). With the combined assumptions of 100% persistence and an additional 10-years offset effect for ZA, ICER's assessment inappropriately overestimates the real-world benefit of ZA.

Finally, ICER focuses on the time on sequenced therapies (i.e., on ZA), which confounds the estimation of value of the bone-forming agents being assessed; time on ZA accounts for 80% of the total treatment period in ICER's assessment.

ICER should simulate real world estimates of persistence of each therapy over time, credible offset effect duration and not focus excessively the attention of the assessment on the time post bone-forming agents to better reflect current clinical reality and assess their value.

5. ICER's model is unstable as demonstrated by the extremely large volatility of its results.

Variations of one single input in ICER's model cause changes on results by millions of dollars per QALY. In the case illustrated above (issue #2), when the use of non-vertebral fracture rates to model hip fractures is reversed, the results are approximately 15 times or \$4M/QALY better for romosozumab. However, ICER does not make an appropriate use of probabilistic sensitivity analyses to examine the joint uncertainty in parameters thus putting too much emphasis on point estimates that are greatly uncertain. This results in overly strong conclusions disconnected from the high uncertainty around key parameters and assumptions made.

Correcting the above-mentioned additional issues results in romosozumab being cost-effective according to generally accepted willingness-to-pay thresholds.

Amgen Modeling

Amgen, in collaboration with external experts, have replicated ICER's cost-effectiveness model, despite the scarcity of details provided, and also created a de-novo model based on published models. The former was used to estimate the extent of the impact of the assumptions and data input choices made by ICER in the results, which helped confirm the issues illustrated above. The latter was used to simulate relevant comparisons using clinically relevant inputs and assumptions and demonstrates that romosozumab would provide good value for patients, healthcare systems and society as a whole, and will be subject of upcoming publications.

The correction of the flaws in the ICER assessment is strongly recommended to ensure an appropriate valuation of bone-forming agents for osteoporosis in postmenopausal women in need of rapid bone formation. To provide full transparency, ICER should make their model more transparent and accessible.

Conclusion

Amgen urges ICER to address the above-noted critical flaws that compromise its draft report for osteoporosis. A more credible value assessment will align its methods, inputs and assumptions with health economic good research practices, with clinical guidelines and real-world clinical practice, based on an understanding of the biology of osteoporosis and patient considerations.

In addition, ICER should remove romosozumab completely from this assessment given that additional data will be included in the FDA submission and market approval is no longer expected in 2017.

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Amgen And UCB Announce Top-Line Phase 3 Data From Active-Comparator Study Of EVENITY™ (Romosozumab) In Postmenopausal Women With Osteoporosis

ARCH Study Met Primary and Key Secondary Endpoints by Reducing the Incidence of New Vertebral, Clinical and Non-Vertebral Fractures

Imbalance in Cardiovascular Events Observed as New Safety Signal

THOUSAND OAKS, Calif. and BRUSSELS, May 21, 2017 /PRNewswire/ -- Amgen (NASDAQ:AMGN) and UCB (Euronext Brussels: UCB) today announced that the EVENITY™* (romosozumab) ARCH study met both primary endpoints and the key secondary endpoint. At the primary analysis, treatment with EVENITY for 12 months followed by alendronate significantly reduced the incidence of new vertebral fractures through 24 months, clinical fractures (primary endpoints) and non-vertebral fractures (key secondary endpoint) in postmenopausal women with osteoporosis at high risk for fracture, compared to alendronate alone. An imbalance in positively adjudicated cardiovascular serious adverse events was observed as a new safety signal (2.5 percent EVENITY versus 1.9 percent alendronate at 12 months).

"The efficacy results from this study comparing EVENITY to an active control are robust. At the same time, the newly observed cardiovascular safety signal will have to be assessed as part of the overall benefit:risk profile for EVENITY," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen. "Together with UCB, we will engage with global regulators and medical experts in the field to conduct a thorough evaluation of these data."

EVENITY is an investigational bone-forming agent that rapidly increases bone formation and reduces bone resorption simultaneously, increases bone mineral density and reduces the risk of fracture. In this study, women received subcutaneous injection of EVENITY monthly for 12 months followed by oral alendronate weekly for at least 12 months. At 24 months, women in the EVENITY treatment group experienced a statistically significant 50 percent reduction in the relative risk of a new vertebral (spine) fracture compared to those receiving alendronate alone. Women in the EVENITY treatment group also experienced a statistically significant 27 percent reduction in the relative risk of clinical fracture (non-vertebral fracture and clinical vertebral fracture) at the primary analysis. Additionally, non-vertebral fractures were statistically significantly reduced by 19 percent in the EVENITY treatment group, including a nominally significant reduction in hip fractures.

"We are impressed with the statistically significant superior fracture risk reduction of EVENITY over alendronate, a current standard of care in osteoporosis. When we think that patients who have had a fracture are highly likely to suffer another one, the importance of post-fracture care cannot be emphasized enough," said Iris Loew-Friedrich, UCB's chief medical officer. "We are working on understanding the observed cardiovascular safety signal and will continue to discuss these results with global regulators and experts in the field."

Overall adverse events and serious adverse events were generally similar between the treatment groups throughout the study and also in the initial 12-month EVENITY treatment period. In the initial 12-month EVENITY treatment period, the three most commonly reported adverse events in both arms were nasopharyngitis, back pain and arthralgia. Injection site reactions were reported in 4.4 percent of patients in the EVENITY treatment group and 2.6 percent in the alendronate group during the initial 12-month period. Most injection site reactions were reported as mild in severity. During the open-label alendronate period, there were two positively adjudicated events of osteonecrosis of the jaw, one in a

patient treated with EVENITY followed by alendronate and one treated with alendronate alone. There were six patients with positively adjudicated events of atypical femoral fracture during the open-label alendronate period (two patients treated with EVENITY followed by alendronate and four treated with alendronate alone). The patient incidence of positively adjudicated cardiovascular serious adverse events at 12 months was 2.5 percent in the EVENITY group compared to 1.9 percent in the alendronate group. No imbalance in cardiovascular serious adverse events was seen in the 7,180-patient placebo-controlled FRAME study.

Regulatory submissions for EVENITY based on the FRAME study results are currently under review with the U.S. Food and Drug Administration (FDA), Health Canada and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. 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 EVENITY in the U.S. to occur in 2017. Engagement with PMDA and Health Canada will occur as part of the ongoing review process. The preparation for the European regulatory submission will continue as planned. Further analysis of the Phase 3 ARCH study data is ongoing and will be submitted to a future medical conference and for publication.

About EVENITY

EVENITY is an investigational bone-forming monoclonal antibody and is not approved by any regulatory authority for the treatment of osteoporosis. It is designed to work by inhibiting the activity of sclerostin and has a dual effect on bone, increasing bone formation and decreasing bone resorption. EVENITY is being studied for its potential to reduce the risk of fractures in an extensive global Phase 3 program. This program includes two large fracture trials comparing EVENITY to either placebo or active comparator in more than 10,000 postmenopausal women with osteoporosis. Amgen and UCB are co-developing EVENITY.

About the ARCH study

ARCH (Active-controlled FraCture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture) is a Phase 3 multicenter, international, randomized, double-blind, alendronate-controlled study of EVENITY in postmenopausal women with osteoporosis at high risk for fracture based on previous fracture history. The study evaluated 12 months of EVENITY treatment followed by at least 12 months of alendronate treatment, compared with alendronate treatment alone. The purpose of this study was to determine if EVENITY treatment is effective in reducing the incidence of clinical fracture (non-vertebral fracture and clinical vertebral fracture) and new vertebral fracture. The incidence of clinical fracture was event-driven and the primary analysis occurred when 330 fractures occurred or the last patient was on the study for 24 months, whichever was later.

Patients (4,093) were randomized 1:1 to receive either 210 mg EVENITY subcutaneously every month or 70 mg alendronate orally every week for the duration of the 12-month double-blind alendronate-controlled study period. After the double-blind active-comparator study period, patients received alendronate while remaining blinded to their initial treatment assignment.

About the FRAME study

FRAME (FRActure study in postmenopausal woMen with ostEoporosis) is a multicenter, international, randomized, double-blind, placebo-controlled, parallel-group study in postmenopausal women with osteoporosis, defined as low bone mineral density at the total hip or femoral neck. The study evaluated the effectiveness of EVENITY treatment, compared with placebo, in reducing the risk of new vertebral fractures through 12 months. The study also further evaluated if EVENITY treatment for 12 months followed by denosumab treatment for 12 months, compared with placebo followed by denosumab treatment, was effective in reducing the risk of new vertebral fractures through 24 months.

In addition, clinical fracture (a composite endpoint which encompasses all symptomatic fractures, both non-vertebral and painful vertebral fractures) risk reduction, non-vertebral fracture (fractures outside of the spine, excluding sites that are not considered osteoporotic, fractures due to high trauma or pathological fractures) risk reduction and other endpoints were assessed at 12 and 24 months.

7,180 patients were randomized 1:1 to receive either 210 mg EVENITY subcutaneous (SC) monthly (QM) or placebo SC QM for the 12-month double-blind study period. After the placebo-controlled study period, patients entered the open-label phase where all patients received 60 mg denosumab SC every six months (Q6M) for 12 months, while remaining blinded to initial treatment. An additional 12 month extension period of open-label 60 mg denosumab SC Q6M is currently ongoing.

About the Amgen and UCB Collaboration

Since 2004, Amgen and UCB have been working together under a collaboration and license agreement to research, develop and market antibody products targeting the protein sclerostin. As part of this agreement, the two companies continue to collaborate on the development of EVENITY for the treatment of osteoporosis. This gene-to-drug project demonstrates how Amgen and UCB are joining forces to translate a genetic discovery into a new medicine, turning conceptual science into a reality.

About Amgen

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/amgen.

About UCB

UCB, Brussels, Belgium (www.ucb.com) is a global biopharmaceutical company focused on the discovery and development of innovative medicines and solutions to transform the lives of people living with severe diseases of the immune system or of the central nervous system. With more than 7 500 people in approximately 40 countries, the company generated revenue of €4.2 billion in 2016. UCB is listed on Euronext Brussels (symbol: UCB). Follow us on Twitter: @UCB_news

Amgen Forward-Looking Statements

This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including its most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and Form 8-K. Unless otherwise noted, Amgen is

providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those Amgen projects. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for Amgen to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and Amgen expects similar variability in the future. Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints Amgen has selected. Amgen develops product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as Amgen may have believed at the time of entering into such relationship. Also, Amgen or others could identify safety, side effects or manufacturing problems with its products after they are on the market.

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This press release contains forward-looking statements based on current plans, estimates and beliefs of management. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including estimates of revenues, operating margins, capital expenditures, cash, other financial information, expected legal, political, regulatory or clinical results and other such estimates and results. By their nature, such forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and assumptions which could cause actual results to differ materially from those that may be implied by such forward-looking statements contained in this press release. Important factors that could result in such differences include: changes in general economic, business and competitive conditions, the inability to obtain necessary regulatory approvals or to obtain them on acceptable terms, costs associated with research and development, changes in the prospects for products in the pipeline or under development by UCB, effects of future judicial decisions or governmental investigations, product liability claims, challenges to patent protection for products or product candidates, changes in laws or regulations, exchange rate fluctuations, changes or uncertainties in tax laws or the administration of such laws and hiring and retention of its employees. UCB is providing this information as of the date of this press release and expressly disclaims any duty to update any information contained in this press release, either to confirm the actual results or to report a change in its expectations.

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Moreover, sales may be impacted by international and domestic trends toward managed care and health care cost containment and the reimbursement policies imposed by third-party payers as well as legislation affecting biopharmaceutical pricing and reimbursement.

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May 30, 2017

RE: Comments on Draft Evidence Report “Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value”

Eli Lilly and Company appreciates the opportunity to respond to ICER’s Draft Evidence Report, ‘Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value’. We believe that to be a sound value determination, efforts must be comprehensive and truly patient-centered. Thus we offer the following comments:

Comments on the Draft Evidence Report:

[1] Network Meta-Analysis (NMA).

The NMA was conducted using the main study publications for teriparatide (Neer RM; NEJM 2001), abaloparatide (Miller PD, JAMA; 2016) and romosozumab (Cosman F; NEJM 2016). These studies estimate efficacy for vertebral and “non-vertebral/other” fractures. We have the following comments regarding this particular NMA.

- (1) The definitions for each fracture site across studies are not consistent in the NMA.
 - a. For vertebral fractures, the approach recommended by FDA is to assess lateral spine radiographs using a combination of quantitative morphometry (QM) and semi-quantitative (SQ) assessment, and this approach was used in the zoledronic acid Horizon Trial (Black DM 2007) and in most other osteoporosis studies. The abaloparatide trial used a SQ with SQ confirmation approach (Miller 2016), which is considered similar (Harry Genant, personal communication), and the radiographs were assessed in blinded fashion so that the vertebral fracture data in the abaloparatide study should not be subject to bias. However, the method initially used in the teriparatide Fracture Prevention Trial (FPT, Neer 2001) used a single SQ reading, a less rigorous definition of fractures, and this methodology includes putative fractures which would not be confirmed during a confirmation step, introducing “noise” and reducing biological signal. To be consistent, the teriparatide data from the FPT using the QM+SQ method (Prevrhal 2009) should be included in the NMA. Some important methodological points about the Prevrhal et al. analysis include:
 - i. The original Neer publication from the Fracture Prevention Trial reported single SQ readings performed in blinded fashion by radiologists under the supervision of Dr. Genant. However, The Fracture Prevention Trial protocol included text recognizing that other definitions of vertebral fracture might be employed to assess the radiographs.
 - ii. The quantitative morphometry was performed by a trained and validated central reader blinded to group assignment using in-house (Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA) software under the supervision of Dr Prevrhal.
 - iii. Working with Dr. Dennis Black, a statistical analysis plan was approved prior to the completion of the QM assessments. The statistical analysis plan described the definition of fracture, defined how missing data would be handled, and specified all aspects of the statistical analysis.
 - b. Non-vertebral fragility fracture is the standard endpoint in most osteoporosis studies, and excludes fingers, toes, face, skull, and traumatic or pathological fractures (Krege and Wan 2012). While this is the correct endpoint, the assessment of whether fractures are due to fragility must be performed in blinded fashion to avoid bias. ICER should not compare unblinded, nonvertebral fragility fracture data for teriparatide from the abaloparatide ACTIVE trial to blinded data from other studies. Although ICER did run a sensitivity analysis excluding these open label data, the base case should exclude the unblinded open-label teriparatide data from the abaloparatide study.
- (2) Although the Draft Evidence Report relied on the traditional PICOTS format, the patient populations of the 3 anabolic studies used in the NMA were widely heterogeneous in terms of prior vertebral fracture (100% [FPT], 24% [ACTIVE], and 18% [FRAME]); and mean BMD T-scores at the total hip (-2.6 [FPT], -1.9 [ACTIVE], and -2.5 [FRAME]). The

higher incidence of reported fractures in the control group of the FPT further indicates that the patient populations included in the teriparatide study were at 2-4 times higher risk (see Table 7, p.26), and thus not comparable to patients included in the other trials pooled for the NMA.

- (3) The NMA used a fixed effect model and assessed goodness of fit and heterogeneity using deviance information criterion (DIC) and residual deviance (resdev). A fixed effect model (as used by the authors) assumes that there is a single true effect of the intervention which is common across all studies. However, given the noted heterogeneity between the baseline characteristics of patient populations, the fact that each of the three included studies examined different interventions, as well as the wide range of reported treatment effects, it is highly unlikely that a fixed effects model would be appropriate. Thus, a random effects model should be considered for the NMA. Additionally, as the authors did not report out the results of their model fit parameters (DIC or resdev) it is impossible to assess whether the model and subsequent results appropriately characterize the combined and relative effects of the intervention.

[2] Teriparatide's Real-World Evidence (RWE).

The Draft Evidence Report does not appear to take into consideration the large body of RWE on teriparatide's safety and effectiveness. In Section 5, Other Benefits or Disadvantages, the report concludes there are no differences between drugs in terms of their impacts on "individual patients, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness." The lack of RWE for abaloparatide or romosozumab should not be a justification for ignoring teriparatide's RWE. Lilly strongly recommends that ICER take into account the long history of real-world safety evidence, its real-world fracture evidence, and other real-world outcomes. The RWE on fracture effectiveness supports the findings from the FPT, and extends those results in the case of hip fractures, despite the numerous challenges and limitations associated with heterogeneous patient populations, suboptimal adherence to therapy, wide variations in clinical practice, and with incomplete information on clinical risk factors.

- (1) Non-vertebral fracture effectiveness.
 - a. NV fracture relative risk reductions from large prospective observational studies range from 45% to 38% (45%-38% Langdahl B, 2009 [EFOS study]; 43% Silverman S 2012 [DANCE study, Mo. 18-24 vs. Mo. 0-6])
- (2) Hip fracture effectiveness
 - a. Hip fracture relative risk reductions range from 56% to 45% (Silverman S 2017 [pooled observational study data from EFOS, ExFOS, DANCE, JFOS (56% reduction in hip fracture events); Burge RT .2017 [retrospective claims database analysis on teriparatide's hip fracture efficacy (OR = 0.55; 95% CI, 0.42, 0.74) and was based on 149 hip fracture events].
- (3) Clinical vertebral fracture effectiveness.
 - a. Clinical vertebral fracture relative risk reductions range from 73% to 40% from retrospective claims database studies (73%-61%, Yu S 2012; 40%, Burge RT 2017); and an estimate of 62% from EFOS (Langdahl B, 2009).

These fracture reduction effectiveness estimates, and particularly for hip fracture where data have been lacking, could be included in sensitivity analyses in the model.

Other RWE results from EFOS include improvements in back pain (decrease in bed days due to back pain; and decrease in back pain; Fahrleitner-Pammer et al 2011; decrease in frequency and severity in back pain (Aloumanis 2011); decrease in limitations of activities (Aloumanis 2011); improved mobility (Aloumanis 2011); and decreased pain and discomfort (Aloumanis 2011). In a U.S. claims database study, reductions in fragility fracture risk for teriparatide patients compared to matched non-teriparatide controls was seen as early as 6 months and continued up to 24 months [Boytsov N 2015]. In addition, fracture-related hospitalizations were 30% to 45% lower among teriparatide patients with borderline statistical significance during 12 and 18 months of follow-up and became statistically significant at 24 months. Fracture-related ER visits were 67%, 69%, 62% and 59% lower over 6, 12, 18 and 24 months of follow-up, respectively, among teriparatide patients vs. a matched non-teriparatide cohort.

[3] VERO head-to-head trial (teriparatide vs. risedronate)

The VERtebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) trial (NCT01709110) compares teriparatide to risedronate 35mg once weekly. The study was a randomized, double blind, and double dummy active comparator study, and the primary endpoint was the proportion of patients with new morphometric vertebral fractures at 24 months. The topline data from this study were disclosed at the WCO-IOF in March 2017 (Kendler D et al.). After 2 years, fewer patients had new vertebral fractures in the teriparatide group compared to risedronate (5.4% vs 12.0%, $p < 0.0001$; RR = 0.44 [0.29; 0.68]), and after 1 year (3.1% vs 6.0%, $p < 0.05$). The relative risk for teriparatide vs. risedronate for other fracture endpoints included: moderate/severe

vertebral fractures 0.42 (0.27; 0.65); multiple vertebral fractures 0.16 (0.04; 0.74); and clinical fractures (vertebral + non-vertebral) 0.48 (0.32; 0.74). Lilly recommends that ICER include this important H2H study in its assessment.

[4] Analytic base case.

1. The cost-effectiveness model compares the three anabolic therapies to IV zoledronic acid bisphosphonate (BP) in the base case. A more realistic base case would consider actual real-world place in therapy for teriparatide (and newer injectable therapies), whereby substantial access barriers exist in the form of Prior Authorizations that often require lower BMD, previous fractures, and prior BP use. Following teriparatide usage, treatment with an antiresorptive therapy is recommended to help maintain the gains in bone mass from teriparatide and low rate of fracture. Available data show that antiresorptive agents increase BMD after teriparatide cessation (see for example, Prince R 2005, Leder BZ 2015). Importantly, the fracture rate after stopping teriparatide treatment remains low (Prince R 2005, Silverman S 2013, Fahrleitner-Pammer A 2011). Therefore, the base case should compare anabolics followed by an antiresorptive therapy as a sequence to each other and no treatment, while in a secondary analysis comparisons to BPs could be asconducted.
2. In the cost-effectiveness analysis (CEA), the authors “assumed the fracture risk was similar to that observed in the clinical trials of the anabolic agents” and used a single baseline risk across the entire CEA. This is inappropriate for the reasons outlined above, that the baseline characteristics and risks for fracture were significantly different for patients in the Fracture Prevention Trial compared to the other 3 included studies. By pooling the annual fracture probabilities from the pooled placebo arms across the three studies, the authors may have biased the results to favor the effects of trials that included lower risk patients. The higher risk of fracture in the placebo arm of the Fracture Prevention Trial may increase the reported effect for trials that included lower risk patients.

[5] Health utilities for non-clinical vertebral fractures.

The Draft Evidence Report applies health utility decrements for clinical vertebral fractures (comprising 35% of all vertebral fractures), and no utility decreases for non-clinical vertebral fractures. However, non-clinical vertebral fractures have been associated with utility decreases, though at about one-third the impact from clinical vertebral fractures (Hiligsmann 2008; Kanis JA 2004; Cockerill W 2004), and should be used in the model to calculate QALYs.

[6] Other comments on the Draft Evidence Report.

ICER Table 4. The morphometric vertebral fracture data should use the data reported by Prevrhal et al. 2009

Table E4. Under the “measurements equal and valid column”, the Neer study used a different assessment. Instead, the Prevrhal 2009 study should be used in this table and in the NMA.

Table E5. Nonvertebral fragility fractures were 6% in placebo, and 3% in the teriparatide 20 mcg/day group.

Table E6. The vertebral fracture data for teriparatide should use the data reported in Prevrhal 2009 to be consistent with the SQ with QM confirmation from the zoledronic acid study, and the SQ with SQ confirmation from the abaloparatide study.

Table E8. It is not believable that abaloparatide has a 95% reduction in hip fracture, when the data are based on 2 fractures in placebo vs. 0 on abaloparatide. There should not be a ranking of the drugs.

Table E9. The data for teriparatide are from single SQ readings (reported in Neer 2001). A better endpoint is QM plus SQ confirmation, which is reported in Prevrhal et al. 2009.

In Table F1. Detailed Results Per Regimen, the results from the probabilistic sensitivity analysis (PSA) are given. It would be helpful to readers to supplement this table with scatterplots.

Description of abaloparatide. On page 6, abaloparatide is described as “Abaloparatide is a new PTH analog, approved by the FDA on 4/28/17, and is similar to teriparatide.” The precise description, as contained in the TYMLOS label, should be used in order to correctly provide these important differences between molecules: “TYMLOS injection for subcutaneous administration contains abaloparatide, a synthetic 34 amino acid peptide. Abaloparatide is an analog of human parathyroid hormone related peptide,

PTHrP(1-34). It has 41% homology to hPTH(1-34) (human parathyroid hormone 1-34) and 76% homology to hPTHrP(1-34) (human parathyroid hormone-related peptide 1-34).”

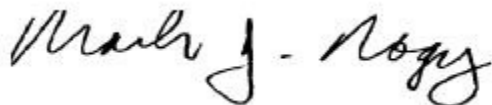
Harms. The TYMLOS (abaloparatide) label is now available: During the first month of the trial, injection site reactions were assessed daily one-hour after injection. TYMLOS had a higher incidence than placebo of injection site redness (58% vs. 28%), edema (10% vs. 3%) and pain (9% vs. 7%). Severe redness, severe edema, and severe pain were reported in 2.9%, 0.4%, and 0.4% of the TYMLOS-treated patients.

Of the patients receiving TYMLOS for 18 months, 49% (300/610) developed anti-abaloparatide antibodies; of these, 68% (201/297) developed neutralizing antibodies to abaloparatide. Of the patients with anti-abaloparatide antibodies tested for cross-reactivity, 2.3% (7/298) developed cross-reactivity to PTHrP, 43% (3/7) developed neutralizing antibodies to PTHrP, and 0% (0/298) developed cross-reactive antibodies to PTH. Antibody formation did not appear to have any clinically significant impact on safety or efficacy endpoints, including bone mineral density (BMD) response, fracture reduction, immune-related hypersensitivity or allergic reactions, or other adverse events. Most of the patients with anti-abaloparatide antibodies during treatment with TYMLOS, 85% (256/300), had follow-up antibody measurements six months after completion of TYMLOS therapy. Among these patients, 56% (143/256) remained antibody positive.”

Also, abaloparatide was reported to cause tachycardia in the ACTIVE clinical trial; increasing heart rate by 15 beats/minute (TYMLOS package insert).

We appreciate efforts to create a transparent method for assessing value; however, we strongly believe 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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Mr. Matt Seidner
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Re: Request for input on the Osteoporosis Draft Evidence Report posted on May 3rd, 2017

Dear Mr. Seidner:

Radius Health, Inc. is pleased to provide the following comments related to the ICER request for input on the Osteoporosis Draft Evidence Report.

Osteoporosis is a serious and costly disease. Nearly one in two women will experience an osteoporosis-related fracture in her lifetime (Harvey et al., 2008). An estimated two million osteoporotic fractures occur annually in the United States, and this number is projected to grow to three million by 2025, with direct costs expected to surpass \$25 billion (Dempster et al., 2011). Hospitalizations for osteoporotic fractures are higher than that of stroke or heart attack or breast cancer (Singer et al., 2015). Despite the growing prevalence of osteoporosis and related fractures over the past decade, more than half of the postmenopausal women with osteoporosis fracture remain undiagnosed, untreated or are limited in their access to affordable appropriate treatment, and there have been very few new agents introduced to treat these patients (National Committee for Quality Assurance, 2016).

Osteoporosis is also a complex disease in which different classes of medicine play fundamentally different roles biologically and in the treatment paradigm. Radius Health believes that any meaningful value framework must recognize the distinctions between drugs and drug classes, or risk being deeply flawed and worse will raise access barriers to the very women it is intending to help. ICER's draft evidence report is misaligned with real-world clinical practice and osteoporosis treatment guidelines. These guidelines differentiate between anabolic agents for their bone building mechanisms and their efficacy benefit of the reduction of both vertebral and non-vertebral fractures in patients at high risk for fracture and the maintenance role of bisphosphonate agents (Camacho et al., 2016). TYMLOS™ (Abaloparatide-SC injection) is the first new anabolic agent available to postmenopausal women with osteoporosis in nearly 15 years. TYMLOS is a human parathyroid hormone related peptide [PTHrP (1-34)] analog 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. In postmenopausal women with osteoporosis, TYMLOS reduces the risk of vertebral fractures and nonvertebral fractures (TYMLOS Prescribing Information, April 2017).

The disconnect between osteoporosis and related fractures is an escalating and often overlooked health crisis (Giangregorio et al., 2006). Nonvertebral fractures represent the clear majority of all fractures (73%) and costs (94%) (Burge et al., 2007), and yet, many postmenopausal women – especially younger ones in their 50s – fail to make the connection that seemingly insignificant fragility fractures (i.e., wrist) could be a warning sign for disease progression and that early intervention can reduce the risk of subsequent fractures.

Our priorities include ensuring a fracture is truly viewed as a sentinel event, requiring early intervention, which can reduce the risk of future fractures. Further, Radius is committed to raising awareness of the issues of under diagnosis and undertreatment of this devastating disease and overcoming the barriers to access and affordability for postmenopausal osteoporotic women who have experienced a recent fragility fracture or who are at high risk for fracture. In response to ICER's invitation to provide input regarding the draft report, we would like to offer the following for consideration:

1) Current Crisis in Osteoporosis Management: Osteoporosis remains significantly under treated

Many osteoporosis patients at risk of fractures remain untreated. Recent evaluation of Medicare data suggests that the plateauing of age-adjusted temporal reduction in hip fractures may be associated with the decline in testing and treatment of osteoporosis (Khosla and Shane, 2016). Unfortunately, patients discharged with a hip fracture from hospitals today remain under-treated compared to those discharged with other major events (i.e., myocardial infarction). The undertreatment may also be due in part to negative media reports associated with the risk of rare but serious adverse events with bisphosphonates including osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF) (Yood et al., 2008). In 2010, the FDA issued a global warning regarding these safety risks early in treatment, which may have contributed to a 50% decline in use of these agents (FDA 2010 warning-FDA website). To overlook these causes of morbidity and resultant lack of adherence in today's treatment paradigm as part of any cost effectiveness model would be an omission affecting the validity of the model's outcomes.

A recent evaluation of medical and pharmacy claims data from a large, geographically diverse cohort of private commercial and Medicare Advantage plans with no prior history or treatment of osteoporosis who experienced a new hip fracture (n=8,349) further documents the gap between evidence-based guidelines and reality. Of women who experienced a hip fracture, only 17.1% and 23.1% had evidence of osteoporosis assessment and/or treatment within 6 or 12 months of their fracture respectively (Gillespie and Morin, 2017). Hip fractures are considered "non-vertebral" and as discussed earlier, nonvertebral fractures in total represent the clear majority of all fractures (Burge et al., 2007).

2) Early therapy of patients at high-risk of fragility fractures is key in reducing osteoporosis morbidity, mortality and associated costs

The importance of early intervention has been consistently supported in several studies. The 12-month period after the first osteoporotic fracture has been noted as the critical year, a key high-risk period requiring interventions to improve patient outcomes.

Prior fracture history is the highest predictor of future fracture risk (Weaver et al., 2016). The rate of repeat fracture within 1 year of the initial fracture based on real-world data varies between 4%-9% and is dependent on the fracture site (Song et al., 2011).

Although there is a high prevalence of vertebral fractures (27%) nonvertebral fractures represent 73% of all fractures and 94% of related costs (Burge et al., 2007). They include wrist (19%), hip (14%), pelvic (7%) and other fractures (humerus, clavicle, and hand/fingers-33%). Looker and colleagues recently provided the first nationally representative estimates of FRAX-based 10-year probability of major osteoporotic fracture (hip, spine, proximal humerus, or distal forearm) for adults aged 50 and over using the 2013-14 NHANES survey. The 10-year probability of major osteoporotic fractures varied from 2.9% for 50-59 age group to 27% for 80+ age group (Looker et al., 2017).

Hip fracture has a significant downstream impact including associated health and economic consequences, which need consideration. Of women over age 50 who sustain a hip fracture approximately 25% of women die in the year following the fracture, 50% never walk independently again and 20% require permanent nursing home placement (U.S. Department of Health and Human Services, 2004). According to a recent Bone Health Index Survey by the National Osteoporosis Foundation (NOF), loss of independence (42%) and lost mobility (25%) ranked as the leading concerns about aging for osteoporosis patients as well as their caregivers' uncertainty about their ability to manage their patient care (50%) (National Osteoporosis Foundation 2016). The burden and cost of disease associated with distal radial fracture has also been significantly underestimated. Patients with distal radial fracture have a much greater risk for subsequent hip fracture within 1 year (HR=3.45) (Litwic et al., 2014). The risk is the greatest in the first month after the distal radial fracture (Chen et al., 2013). However, many postmenopausal women, especially those in their 50s, as well as their treating physicians, fail to recognize that the fragility fractures (e.g., wrist) could be a sentinel event or warning sign for osteoporotic disease progression. For these patients that need immediate fracture prevention alternative treatment options that are specifically designed to build bone are suggested. The use of commonly prescribed bisphosphonates, that only slow bone loss and do not improve or build bone, are simply not enough.

The total cost of care is also significantly higher for those experiencing a subsequent fracture compared to those without a history of prior fracture for both Medicare (\$34,327 vs. \$20,790; $p < 0.001$) and for the commercial health plan enrollees (\$39,501 vs. \$19,131; $p < 0.001$) (Weaver et al., 2016). In a recent study of US managed care enrollees, the -subsequent fracture was estimated to increase medical costs by \$47,351, \$43,238, and \$23,852 for commercial patients with prior hip, clinical vertebral, and non-hip/-nonvertebral (NHNV) fractures and \$18,645, \$19,702, and \$19,697 for Medicare patients respectively. The AACE/ACE guidelines acknowledge the importance of the inclusion of an anabolic therapy for treatment of patients at high risk of fracture, including those with a prior fracture history (Camacho et al., 2016). It is also recognized that the use of anabolic therapies to build bone as early as one month, and not just enhance existing bone mineral density, will have a positive impact on reducing the humanistic and economic burden of subsequent fractures.

3) Limited access to effective therapies for patients at high-risk of fractures will prolong the poor health and economic outcomes

Recent position papers from medical societies include calls to action to: (1) emphasize the importance of early diagnosis and early treatment, (2) highlight the value of shared decision making and customizing treatment in consideration of benefits and risks of individual therapies and patients; and (3) suggest additional approaches to identification and treatment of high risk patients where current healthcare pathways may not be sufficient.

The ASBMR working group suggests a goal-directed treatment for osteoporosis where treatment decision is guided to maximize patient's ability to achieve goal. Osteoporosis treatment goals need to parallel indications for initiating treatment and logical treatment goals are BMD levels above and fracture risk levels below those for which treatment is usually recommended. This Working Group interim report supports the potential value of goal-directed treatment and sets out several principles to guide this approach to selecting and monitoring treatments. Some of these principles such as considering a more potent initial treatment in those with high risk of fracture and continuation or intensification of treatment when a vertebral fracture occurs on therapy could be put into practice now (Cummings et al., 2017).

The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) recognize the importance of anabolic or bone-building agents. The AACE published new guidelines on the treatment of osteoporosis last September (Camacho et al., 2016). It is now recommended that an anabolic agent be used as a first-line treatment for patients at high risk for osteoporotic fracture. And in fact, there is new evidence that sequence of therapies matters, suggesting the use of a bone-building agent (anabolic) followed by an antiresorptive agent, such as a bisphosphonate or denosumab wherever possible to improve bone density and decrease fracture risk in these patients (Cosman et al., 2017).

Finally, the National Committee for Quality Assurance (NCQA) recognized that health care providers often neglect treating patients with osteoporosis including high risk patients and has called for the need to focus on secondary fracture prevention and closing the care gap for testing and treatment for high risk patients (National Committee for Quality Assurance, 2016).

We reiterate our position that ICER should focus on a patient-centered approach that clearly delineates the distinction of patients at high risk for fractures in need of immediate fracture prevention, as well as the need for quality care for that specific patient population that takes into consideration total cost of care, and not limit the analysis to only direct product unit costs without current and comprehensive direct fracture costs and indirect treatment and intolerance costs.

Of interest is the patient consultation and feedback to ICER in the May 3rd report noting that insurance often requires that they fail an oral therapy before authorizing an injectable therapy. Bisphosphonates are often recommended as first line use; however, these agents slow the loss of existing bone but do not build new bone. Osteoporosis is not one disease, and no one treatment will work for everyone. Those who make new bone too slowly need another option, particularly during the first critical year post the initial fracture. We suggest ICER's recommendation consider evidence-based guidelines and to reduce the administrative burden on clinicians and patients supporting early access to targeted therapy for high-risk patients.

In addition to the above considerations, we would also like to reiterate the following requests to correct erroneous assumptions. ICER doing the following is highly encouraged by Radius to ensure a meaningful and accurate value assessment:

- Appropriately compare like agents as they are not designed to do the same things. Therefore:
 - Agents that build bone and demonstrate early fracture reduction, within 2 years, should be compared with others that do the same.
 - Antiresorptives that slow resorption of existing bone, such as zoledronic acid and denosumab, should be compared with other antiresorptives.
 - The guidelines do make a distinction between drug classes in consideration of “patients’ risk of fracture, prior disease, and treatment history” and so ICER should equally take these differences in drug classes into consideration in their model.
- Use WAC instead of net price:
 - Use correct price of TYMLOS vs. the other approved agents at a WAC basis.
 - Consistent with the BIO response to ICER on the “National Call for Proposed Improvements to its Value Assessment Framework” we previously suggested using the WAC which can be easily verified rather than the variable, estimated and unsubstantiated net prices of the prescription drugs in the value assessment methodology.
 - Moreover, use of a net price fails to take into consideration the impact on patient cost-sharing obligations between the agents and the corresponding discontinuation of treatment due to affordability issues. Since manufacturer discounts are not directly passed on to patients, a reduced WAC is the only direct way a manufacturer can lower out of pocket cost for Medicare D patients fostering greater adherence and associated outcomes.
- Use the studied treatment duration for TYMLOS:
 - TYMLOS was approved based on 18 months of treatment, not 24 months of treatment, substantiated by the ACTIVE and ACTIVEExtend trials.
- Incorporate impact of the first demonstrated sequential therapy approach for TYMLOS:
 - TYMLOS approval includes data from two trials, 18 months of using TYMLOS (ACTIVE) (Miller et al., 2016) to demonstrate relative risk reduction of vertebral and non-vertebral fractures followed by the first six months of the use of a bisphosphonate (alendronate) to “build and extend” gains in BMD (ACTIVEExtend) (Cosman et al., 2017).
 - ACTIVEExtend is an important sequential treatment data set to inform physicians and patients how to treat postmenopausal women with osteoporosis and a high risk of fracture.
 - The ICER model should take into consideration this demonstrated treatment paradigm with both its efficacy and safety results.
- When available, utilize data from comparative trials to accurately compare like agents (e.g. anabolics) rather than using cross-study comparisons which have inherent limitations due to study design, inclusion / exclusion criteria, etc.
- Use both event and incremental costs of subsequent fractures as well as the burden to the patients based on peer-reviewed published data.
- Weight each fracture site appropriately, based on prevalence and associated cost so as to not overestimate the impact of hip and underestimate the impact of other fractures.
- Utilize real-world evidence (third party data) to estimate adherence rates as the ICER assumption of 100% is inconsistent with real-world evidence (Yang et al., 2016; Earnshaw et al., 2016; Modi et al., 2016).
- Model serious adverse events (Table 6 in ICER report) to accurately reflect the safety of each of the agents. It is important to not only consider the efficacy of each agent but also their safety profiles. For example: TYMLOS and teriparatide each have boxed warnings for osteosarcoma, a rare but serious adverse event found in preclinical studies in rats, resulting in a cumulative use of no more than two years in a patients’ lifetime. There have been no incidences of osteosarcoma in the human trials conducted for TYMLOS or for

teriparatide (Andrews et al., 2012). Antiresorptives, such as bisphosphonates and denosumab, have rare but serious adverse events of AFF and ONJ. In addition to AFF and ONJ risk, denosumab also carries in its label a warning for multiple vertebral fractures (MVF) following the discontinuation of denosumab treatment, with new vertebral fractures occurring as early as 7 months (on average 19 months) after the last dose. The costs associated with this known risk should be included in the ICER analysis. Any agents with a REMS would also have published data that informs the real-world incidence of any safety events as well. Any published clinical or real-world data that demonstrates the impact of discontinuation on the sustainability of fracture risk reduction should also be taken into consideration in the model (Yang et al., 2016, Earnshaw et al., 2016; Modi et al., 2016). Underestimating safety could risk ignoring the burden this places on patients and any potential hospitalization or resource utilization costs. This must be taken seriously.

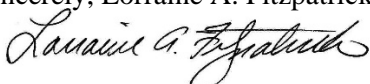
- Agents that have not been approved should not be considered in the model.
- Accurately estimate treatment uptake:
 - ICER must take into consideration current treatment guidelines, levels of payer access, and access restrictions.
 - As suggested to ICER through BIO previously “In addition to using historical data, estimation of new treatment uptake can also consider evidence-based treatment guidelines especially where there is a treatment paradigm change as well as any other quality of care measures that may impact prescribing habits.”

Please also refer to the ASMBR “Call to Action” which cites that new evidence is emerging that the 30-year downward trend in hip fractures in the U.S. has hit a plateau in the last few years, indicating that the field as a whole must take action to aggressively reduce fracture risk in the US aging population. Many experts are now acknowledging that there is a crisis caused by the declining rate of testing, diagnosis and treatment of high-risk patients. Allowing these patients to go untested and untreated frequently leads to debilitating fractures that cause disability, loss of independence and even death. In fact, 25% of women over the age of 50 who sustain a hip fracture die in the year following the fracture, 50% never walk independently again and 20% require permanent nursing home placement (U.S. Department of Health and Human Services, 2004). According to a recent Bone Health Index Survey by the NOF, loss of independence (42%) and lost mobility (25%) ranked as the leading concerns about aging for osteoporosis patients as well as their caregivers’ uncertainty about their ability to manage their patient care (50%) (National Osteoporosis Foundation, 2016).

As one ages, the bone building (or formation) part of the process is often unable to keep up with the bone loss (or resorption) part of the process. In women, estrogen plays a role in regulating the bone formation and resorption process. Women start losing estrogen at menopause, which is accelerated over the initial period during their postmenopausal phase, and contributes to women beginning to lose more bone than they are replacing or building. Left untreated, osteoporosis can lead to bone deterioration throughout the body, leaving patients vulnerable to osteoporotic fracture.

Today, the hospitalizations for osteoporotic fractures are higher than that of stroke or heart attack or breast cancer (Singer et al., 2015). Additionally, osteoporotic fractures account for more hospitalizations and associated costs than cardiovascular disease or breast cancer. Nonvertebral fractures represent the clear majority of osteoporotic fractures as well as the associated costs (Burge et al., 2017). Once a patient has experienced a fracture, the risk of another fracture is highest in the first year, and the patient is 3 times more likely to have another fracture. The risk remains high for the subsequent years (Harvey et al., 2016). Fractures due to osteoporosis are estimated to cost \$25 billion per year by 2025. It is counter to clinical evidence to recommend limiting treatment options to only antiresorptives and not acknowledge the clear clinical data supporting the use of anabolic therapy for postmenopausal women with osteoporosis to reduce their high risk for future fracture.

Sincerely, Lorraine A. Fitzpatrick, MD, FACP, FACE, Chief Medical Officer, Radius Health, Inc.



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May 25, 2017

Steven Pearson, MD
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Dear Dr. Pearson:

The Alliance for the Adoption of Innovations in Medicine (“Aimed Alliance”) is a nonprofit organization that works to expand access to quality health care in the U.S. On behalf of Aimed Alliance, I respectfully submit the following comment in response to the draft evidence report, entitled “Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value” (“Draft Report”) published by the Institute for Clinical and Economic Review (“ICER”).

Osteoporosis is a disease characterized by “low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures of the hip, spine, and wrist.”¹ Osteoporosis can cause bones to become so brittle that a fall or mild stresses, such as bending over or coughing, can result in a fracture, and fractures can result in pain, disability, and death.² Osteoporosis affects 10.2 million older adults in the United States,³ including one-quarter of all American women 65 years or older.⁴

Osteoporosis can have a significant impact on quality of life. For instance, only 25 percent of individuals are able to return to their activities of daily living after experiencing a hip fracture.⁵ Such a fracture can result in an inability to walk and, therefore, loss of independence.⁶ Vertebral fractures can also reduce the ability to perform daily activities and care for oneself or others.⁷ Fractures can have a psychological impact as well, resulting in anxiety, fear, depression, reduced self-esteem, and social isolation.⁸ To prevent bone deterioration and fractures, and improve overall quality of life, individuals with osteoporosis must have access to effective treatment options. However, the Draft Report may limit those options.

QALYs are Discriminatory

The use of quality-adjusted life-years (“QALYs”) to develop a rigid price cap is inconsistent with

¹ *Osteoporosis Overview*, NIH Osteoporosis and Related Bone Disease National Resource Center (June 2015), https://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/overview.asp.

² *Osteoporosis*, Mayo Clinic <http://www.mayoclinic.org/diseases-conditions/osteoporosis/home/ovc-20207808> (last visited May 25, 2017).

³ Nicole C. Wright, *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*, 29(11) *J. Bone Miner. Res.* 2520 (Nov. 2014).

⁴ E.J. Mundell, et al., *1 in 4 Senior Women in U.S. Has Osteoporosis: CDC*, U.S. News & World Report, (Aug. 13, 2015), <http://health.usnews.com/health-news/articles/2015/08/13/1-in-4-senior-women-in-us-has-osteoporosis-cdc>.

⁵ Melisa M. Madureira, et al., *Quality of Life Measurements in Patients with Osteoporosis and Fractures*, 67(11) *Clinics* 1315 (Nov. 2012).

⁶ *Id.*

⁷ *Id.*

⁸ *Id.*

Aimed Alliance

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American values and public policy. Congress added language to the Patient Protection and Affordable Care Act that prohibited the Patient-Centered Outcomes Research Institute (“PCORI”) from using QALYs as a threshold for determining coverage, reimbursement, or incentives in the Medicare program. The ban reflected a long-standing concern that the approach would lead to health care rationing as well as age- and health status-based discrimination, unfairly favoring healthier and younger populations. This is especially problematic when applied to a condition, such as osteoporosis, which disproportionately affects those who are 50 years of age and older.

QALYs put a price tag on the value of a human life that merely reflects an individual’s diagnosis. They treat individuals’ lives and health as a commodity and ignore the patients’ and practitioners’ individualized concept of the value of treatment. Therefore, the QALY should not be used to set a threshold for a large population of individuals with one-of-a-kind life narratives across a complicated health care system. Instead, Aime Alliance urges ICER to consider other methods of valuation, including life years gained, as ICER did in its rheumatoid arthritis report, to measure the benefits of osteoporosis medications.

Prioritizing Access to Options

The goal of osteoporosis treatment is to prevent fragility fractures associated with the disease. In order to meet this goal, patients must have access to the best treatment to repair their bones. To ensure patients receive adequate care, quality and choice of treatment options should not, by default, be sacrificed for cost-saving measures. The United States Court of Appeals for the Ninth Circuit has stated that “[f]aced with such a conflict between financial concerns and human suffering . . . the balance of hardships tips decidedly in [the patients’] favor.”⁹

While patient advocacy groups have noted that step therapy and prior authorization are major barriers to accessing anabolic treatment, suggestions that anabolic therapies are not cost-effective would serve to bolster third-party payers’ use of such policies in direct conflict with patients’ best interest. As a result, patient access to life-saving treatments could decrease. Instead, recommendations must be made that prioritize access to such treatments for individuals for whom they are clinically indicated.

Patient and Practitioner Perspective

Patients must have a meaningful role in the discussion of value given that they are directly impacted by a report that seeks to define the effectiveness and value of their treatment options. Therefore, accounting for how patients define the value of their treatment options should be critical to ICER’s analysis.

While the Draft Report notes that loss of independence and loss of mobility are the top two concerns among patients, it is unclear how these two factors were calculated into the cost-benefit analysis. Moreover, as ICER notes, available studies and clinical trials do not report outcomes most meaningful to patients, including 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. Therefore, adequate studies must be conducted on these important factors before an accurate cost-benefit analysis can be conducted.

Additionally, the current committee lacks health care practitioners and patients with bone health background. It is unclear whether a bone health physician was consulted in drafting the report. And

⁹ Lopez v. Heckler, 713 F.2d 1432, 1437 (9th Cir. 1983).

while patient groups may have been consulted, no one with experience in the bone health field will be voting on the final outcome of this report.

Improper Comparison

The Draft Report compares anabolic therapies to zoledronic acid. Yet, anabolic therapies are designed to build new bones whereas zoledronic acid slows down degeneration. Also, as the Draft Report acknowledges, anabolic therapies are taken for a period of one to two years, whereas zoledronic acid is recommended for longer periods, with a treatment holiday after three years for individuals with low to moderate risk osteoporosis and after six years for individuals at higher risk.

These medications work differently, have different results, and are taken for different periods of time.¹⁰ Moreover, as ICER acknowledges, there was only one head-to-head study of these drugs, and therefore, insufficient data to make such a comparison. As such, anabolic therapies should not be compared to zoledronic acid.

Significance of Hip Fractures

The Draft Report downplays the frequency of hip fractures. Every year, over 300,000 individuals 65 years of age and older are hospitalized for hip fractures.¹¹ This is not an insignificant number given the severity of such fractures. Hip fractures result in chronic pain, reduced mobility, disability, loss of independence, and death.¹² Within one year of a hip fracture, mortality rates are between 20 and 24 percent, 40 percent of individuals are unable to walk independently, and 60 percent require.¹³ As a result of these losses, 33 percent are completely dependent or in a nursing home in the year following a hip fracture.¹⁴ Yet, the Draft Report does not seem to take into account costs associated with assisted living. Therefore, the final report should adequately assess the impact of hip fractures, including their indirect costs.

Conclusion

Thank you for your consideration regarding the Draft Report, and we are available for discussion to address our shared goals of access to high quality health care at a price that accurately reflects public and personal benefits in the Final Report.

Respectfully submitted,

Stacey L. Worthy
Executive Director

¹⁰ <http://buffalonews.com/2017/05/22/another-voice-patients-right-treatments-ordered-doctors/>

¹¹ *Hip Fractures Among Older Adults*, Centers for Disease Control and Prevention (Sept. 20, 2016), <https://www.cdc.gov/homeandrecreationalsafety/falls/adulthipfx.html>.

¹² *Facts and Statistics*, International Osteoporosis Foundation, <https://www.iofbonehealth.org/facts-statistics#category-16> (last visited May 25, 2017).

¹³ *Id.*

¹⁴ *Id.*

Public Comment

**Institute for Clinical and Economic Review of Anabolic Therapies for Osteoporosis
in Postmenopausal Women: Effectiveness and Value**

May 30, 2017

From American Bone Health

**Kathleen M. Cody
Executive Director**

**David B. Karpf, MD
Chair, Medical and Scientific Advisory Board
Stanford University School of Medicine**

It is clear from the Institute for Clinical and Economic Review (ICER) Draft Evidence Report on treatments for osteoporosis that the committee has a solid understanding of the burden of osteoporosis in the United States.

As a community-based organization, American Bone Health works with consumers to improve awareness of osteoporosis and educate them on what to do to prevent bone loss and fractures. During our last national awareness screening event in July 2017, we found that 55% of the participants of Medicare age had not had a bone density test (a covered benefit under Medicare) and only 24% of individuals at high risk for fractures were on a treatment for osteoporosis

This gap in diagnosis and treatment leads us to serious concerns about the unintended consequences that may result from the ICER report.

First, for patients at high risk of fracture, the benefits of osteoporosis treatments, and the favorable benefit/risk ratio, are clearly demonstrated in clinical trial data with large groups of patients. New therapeutic options allow greater flexibility for patients; however, determining the best treatment option is an individual decision best left in the hands of doctors. Patients with certain clinical profiles, including eg, low-turnover osteoporosis, steroid-induced osteoporosis, or adult-onset hypophosphatasia (HPP) may/will benefit from an anabolic agent (and patients with HPP and osteoporosis should never be treated with a bisphosphonate), even if the ICER report does not deem it to be a cost effective option based on the comparative data.

Second, placing an economic “score card” on the available treatment options will likely be seen by insurance companies as guidelines for limiting formularies. This will effectively reduce the ability of physicians to prescribe the most appropriate treatment for their individual patients and continue the practice of allocating the best options only to those individuals who have the resources to pay for them.

As an example of the continued inequity of care in osteoporosis management, in the last two months, our facility has seen three patients from the local clinic population with displaced hip fractures who were unaware of their fracture. Thankfully, these three patients had access to a bone density test through their county insurance plan. Still, it is quite disturbing that it took a preventive screening to discover a serious, potentially deadly fracture. These women should not only have access to screening, but access to the best treatment options to prevent further fractures.



Asian Female Age 68
4/29/2017



Caucasian Female Age 68
3/16/2017



Caucasian Female Age 68
3/18/2017

Finally, the ICER analysis assumed that “a new drug or device that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention.” This way of thinking continues to undermine the crisis that we have with the under diagnosis and under treatment of patients at high risk for fracture.

We must work together with ICER to close the gap between our best evidence-based practices and the dismal care provided our aging population. Together, we can raise awareness of this preventable and treatable disease.

About American Bone Health

American Bone Health is a community-based voluntary health organization mobilizing individuals with effective bone health messages to ensure that osteoporosis can be stopped in two generations. American Bone Health builds capacity for local community outreach through technical support, programs and public awareness campaigns. We engage public advocates for osteoporosis prevention, detection and treatment.



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May 30, 2017

Osteoporosis: Draft Evidence Report

Comments from the Global Healthy Living Foundation and its arthritis community, CreakyJoints

The Global Healthy Living Foundation (GHLF, www.ghlf.org) and its arthritis community CreakyJoints (www.creakyjoints.org), would like to thank you for this opportunity to submit comments on the Osteoporosis: Draft Evidence Report. As we have stated in previous draft report public comments, GHLF remains very concerned about the approach ICER takes when evaluating “value”. Our organization represents patients suffering from chronic diseases, including arthritis and osteoporosis, and we find the lack of the patient perspective and the use of the antiquated QALY measurement incredibly troubling. We believe value means something different to every patient and that treatment decisions should be personal and made between patients and their doctors. We are also concerned by the lack of inclusion of a bone expert among the two clinical reviewers and as a result question the accuracy and validity of this report and perceived conflict of interest created by the source of funding for this report.

We have found that the overwhelming majority of ICER’s reports favor the cheapest cost drug, do not take a long-term cost or outcomes view, and shoehorn analytics into an uncomfortably odd set of comparators. For example, ICER chose the intravenous bisphosphonate zoledronic acid, an established treatment protocol, but one that has obvious patient-centered flaws that make it an inappropriate comparator.

1. Compliance is assumed in the draft evidence report as 100 percent. This is not credible. Although the IV comparator used appears to have better compliance because it is given once yearly vs. the oral protocol,ⁱ there is no credible way to assume 100 percent compliance as ICER’s calculations do.
2. The comparator is not the best drug for people at high risk for fracture. The three drugs evaluated are. They, at varying levels, restore bone mass quickly and are designed to be used to prevent fractures in this high-risk group. Time/value is an appropriate ratio to consider, we believe. If, while on a conventional bisphosphonate, a person suffers a fracture when one of the drugs in the study would have created bone mass quickly and prevented the fracture, what is the value of the conventional bisphosphonate? What is ICER’s acceptable fracture rate while on bisphosphonates and where is the calculation that weighs the cost of these fractures vs. the cost of preventing them? These questions, and other more specific issues, such as whether ICER assumed the benefits of bisphosphonate at treatment initiation vs. when those benefits actually occur.
3. What kind of fractures is ICER valuing? It appears to us that hip fractures have been chosen as the weighted favorite. However, vertebral fractures are more common.^{ii,iii} We are also unsure whether the costs are amortized to 2016 dollars.

Every day, patients look to our organization for help because they do not have access to their medications. Our fear is that insurance companies will cite ICER, and their flawed methodology, when making coverage decisions, further limiting the already poor access to new, innovative, and life changing therapies. While we recognize that actions need to be taken to address the high cost of medications and are appreciative of ICER's transparency of their funding sources, we believe their ties to the insurance industry impedes their ability to create a neutral framework.

ⁱ Sunyecz, J. A. (2010). Zoledronic acid infusion for prevention and treatment of osteoporosis. *International Journal of Women's Health*, 2, 353–360. <http://doi.org/10.2147/IJWH.S7322>

ⁱⁱ Szulc, P., & Bouxsein, M. L. (2011). Overview of osteoporosis: epidemiology and clinical management. *Vertebral fracture initiative resource document*. Retrieved from https://www.iofbonehealth.org/sites/default/files/PDFs/Vertebral%20Fracture%20Initiative/IOF_VFI-Part_I-Manuscript.pdf

ⁱⁱⁱ Cleveland Clinic (2010). *Osteoporosis*. Retrieved from <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/osteoporosis-disease/#bib1>





May 31, 2017

Steven Pearson, MD
President, Institute for Clinical and Economic Review
Boston, MA 02109 USA

Re: Institute for Clinical and Economic Review (ICER) Review of Treatments for Osteoporosis

Dear Dr. Pearson:

The American College of Rheumatology (ACR), representing over 9,500 rheumatologists and health professionals that frequently diagnose and treat osteoporosis, appreciates the opportunity to respond to ICER's draft evidence report on treatments for osteoporosis (OP) in post-menopausal women. The ACR supports efforts to define cost-effective and clinically appropriate strategies to manage patients with OP and therefore we appreciate ICER's work in addressing this important topic. We would, however, like to share some concerns about the methods used to generate the report and point out the potential for serious unintended negative consequences for OP patients.

ICER, in this draft report, relies on clinical trial data as the highest form of evidence. Such studies are entirely appropriate for the purpose of demonstrating efficacy and identifying prominent safety signals. However, because of strict inclusion criteria, the patient populations in clinical trials often fail to adequately represent the complexities of real-world patients. Specialists, including rheumatologists, often take care of such patients and manage severe OP in post-menopausal women who also suffer from complex comorbid conditions and have multiple risk factors for progression of OP and fractures (including glucocorticoid use and rheumatoid arthritis). Clinical trial data must therefore be supplemented with data from "real-world" patient populations in order to arrive at conclusions that have validity and broad applicability in the clinical setting. In this context, we think the preference for clinical trial data predisposes the ICER report to underestimate the value of anabolic therapies.

This shortcoming is reflected in the voting questions that were given to the panelists. The questions define high risk of fracture as being *both* a fragility fracture and T score ≤ -2.5 . First, the presence of a fragility fracture of the spine or hip is sufficient in the absence of a low T score to define high risk. Furthermore, the definition fails to take into account other conditions

as mentioned above that increase the risk of fracture. Thus, the reports takes a very narrow focus on populations in clinical trials while missing the diversity and complexity of patients that rheumatologists see in practice every day.

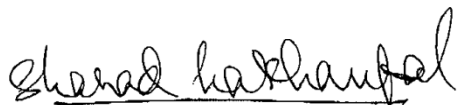
Clinical trial data also frequently fail to capture long-term outcomes and, in the case of OP, a drug's long-term effects on bone architecture. In this way too, the methodology of the ICER report may predispose it to underestimate the benefits of anabolic therapies. Additional risk stratification and sensitivity analysis may have revealed scenarios that better reflect current and medically appropriate use of anabolic therapies in clinical practice.

It should also be noted in the report that anabolic therapies are faster acting and can stabilize a patient more quickly than bisphosphonates – a characteristic of anabolic agents that is of vital importance to patients with severe OP. Furthermore, the model does not consider the importance of published data (Leder B 2015 Lancet 386:1147) that suggest that a patient's response to anabolic agents may be blunted by prior therapy with an anti-resorptive. For this reason, as well as their more rapid onset of action, a clinician and patient may appropriately choose an anabolic agent as first-line therapy in high-risk scenarios.

Finally, we note that only two clinical experts were utilized as reviewers for this effort. We do not believe that this number is adequate for an analysis of this scale and complexity and would like to suggest that the report would have benefited from input from additional experts and practitioners involved in patient care in a variety of settings.

We appreciate ICER undertaking this important task and believe more work is needed to help address the crucial issue of appropriate treatment of patients with OP. The ACR appreciates the opportunity to respond to this report. Please contact Rachel Myslinski, Vice President of Practice, Advocacy and Quality at rmyslinski@rheumatology.org or (404) 633-3777 with any questions or if we can be of any assistance.

Sincerely,

A handwritten signature in black ink that reads "Sharad Lakhanpal". The signature is written in a cursive style and is underlined.

Sharad Lakhanpal, MBBS, MD
President, American College of Rheumatology



May 31, 2017

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ASBMR 2017 Annual Meeting

September 8-11, 2017

Denver, Colorado, USA

Steven Pearson, M.D.
President, Institute for Clinical and Economic Review
2 Liberty Square
Boston, MA 02109 USA

Re: Institute for Clinical and Economic Review (ICER) Review of Treatments for Osteoporosis

Dear Dr. Pearson:

The American Society for Bone and Mineral Research (ASBMR) appreciates the opportunity to respond to ICER's draft evidence report document titled "Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value." The report has the potential to serve as a "wake up call" to address the current crisis in the under-treatment of osteoporosis by examining the value of new therapies. However, we have concerns about the timing of the report, given the current landscape, and the availability of evidence upon which analyses can be conducted at this time. We appreciate the dialogue we have had to date with ICER staff and the National Bone Health Alliance (NBHA) Work Group, which ASBMR co-chairs with the National Osteoporosis Foundation (NOF), and we look forward to our continued dialogue. While we fully support the NBHA's comments, we also wish to offer the following comments on behalf of the ASBMR:

Timing of Report and Paucity of Data

The ICER report is a comparative analysis of the effectiveness and cost effectiveness of two new anabolic osteoporosis therapies (abaloparatide and romosozumab) as well as an established one (teriparatide) compared to the antiresorptive medication, zoledronic acid. Unfortunately, as the report's authors point out, there is currently very limited comparative efficacy data on which to draw conclusions. Instead, the report relies primarily on a limited number of placebo controlled trials and utilizes a network meta-analysis approach requiring numerous assumptions. We feel that this is problematic for several reasons. First, while there are limited published comparative efficacy data that include a fracture efficacy endpoint, there are several studies that do compare anabolic therapies directly to antiresorptives with validated surrogate endpoints such as bone mineral density (BMD) that could have provided additional data to consider. Moreover, given that there are currently 2 completed comparative efficacy trials – VERtebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) and ARCH (Active-controlled FraCture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture) – that, when published, will likely provide some of the most pertinent data on which to base any conclusions, it seems prudent that ICER delay such a report until after this data becomes available.

ASBMR Comments to ICER Page 2

Moreover, the recent announcement regarding potential safety concerns with romosozumab that will delay its FDA approval also supports the impression that the current report may be significantly premature.

Long Term Benefits of Anabolic Therapies and Importance of Drug Sequence

The current analysis in the draft report, which assesses benefits for only up to 5 years, does not take into account the potential for long-term benefits of anabolic therapies. The analysis also does not take into account that virtually all patients who are treated with anabolic agents are treated with antiresorptives at some point in their treatment course as well. Thus an analysis that assumes a single course of anabolic therapy is of limited clinical relevance. Finally, the report does not appear to recognize the growing body of evidence that the sequence in which anabolic and antiresorptive therapies are administered has a profound effect on resultant bone strength. To illustrate this point, it was recently reported in a randomized controlled trial that 2 years of teriparatide followed by 2 years of the antiresorptive, denosumab, increased femoral neck BMD by over 8% in postmenopausal women whereas the same drugs given in the opposite order resulted in a femoral neck BMD increase of less than 5%, which was statistically significantly lower¹.

Voting Questions

The questions for the panel appear to be overly-simplified and do not adequately address the long term value of anabolic agents in the context of a patient's long-term treatment course with multiple agents. Questions should be added to address the value of this approach.

Expert Review

The process of peer review is an underlying fundamental of the scientific endeavor. This report should not be published without that type of rigorous external peer review that we all abide by. There were only two clinical expert reviewers for this report and we believe that it would benefit from having additional input from physicians from multiple specialties, including those with extensive real-world experience in the treatment of osteoporotic patients.

The American Society for Bone and Mineral Research appreciates the opportunity to provide comments on this report and to have ongoing dialogue to result in the most meaningful report possible, given the great need in the field. Please contact Douglas Fesler, Associate Director, at dfesler@asbmr.org or (202) 367-2341 with any questions.

Sincerely,



Jane A. Cauley, DrPH
ASBMR President

¹Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, Burnett-Bowie SA. *Lancet*. 2015 Sep 19;386(9999):1147-55. doi: 10.1016/S0140-6736(15)61120-5. Epub 2015 Jul 2. PMID: 26144908).



May 31, 2017

To: Institute For Clinical and Economic Review.
Subject: Anabolic Therapies for Osteoporosis in Postmenopausal Women:
Effectiveness and Value.

We again applaud this initiative undertaken by the Institute For Clinical and Economic Review. Systematic review of clinical trials and controlled cohort studies with a view to evaluating the effectiveness and value of the anabolic therapies for osteoporosis in postmenopausal women will provide valuable insights to those health professionals who serve patients suffering from fractures that often result from this condition.

The question we must ask is: what conditions must be met for ICER to conclude that the evidence is inadequate to address comparative clinical effectiveness and value at this time?

We urge you to reconsider making any recommendation based on the methodologies you employed to evaluate evidence on effectiveness and value for anabolic therapies for osteoporosis in postmenopausal women. The only empirically supportable recommendation you can make is that further studies are needed. It would help to include details on proposed study designs.

Your Draft Evidence Report can be summarized as follows.

First, there are only three studies which meet your evidence requirements. Each of them compares a single drug to placebo. No studies compare drugs to one another. “Comparative Effectiveness” of any drug to any other drug is generated as a probabilistic projection based on statistical features extracted from the three drug vs. placebo studies. The cited three drug trials also have significant sample-selection constraints on the clinical and demographic variability of patients studied. Is ICER seriously recommending anything to clinicians in the utter absence of germane evidence for the specific clinical decision to select a single agent to treat a far more diverse patient population? Consider the form this might take:

(ICER to doctor): “Abaloparatide, Teriparatide and Romosozumab are clinically not different.”

(doctor to ICER): “How do you know?”

(ICER to doctor): “Probabilistic projections from three drug vs. placebo trials.”

(doctor to ICER): “Sounds like you don’t know enough to make any recommendations.”

(ICER to doctor): “Yeah, but we have a great methodology!”

Second, much effort was devoted to the study of payor osteoporosis policies. However, payor policies can be—and often are—changed at a moment’s notice. Moreover, payors frequently aggressively incentivise clinical decision making in a fashion that minimizes short-term expense,



with little or no regard to improving long-term patient outcomes. Physicians in our group frequently report that payors deny approval, despite conditions being met for prior authorization. Not infrequently, prior authorization is received and then payment is clawed-back later. How payor policies actually manifest themselves in a population of real-world patients is dramatically more important. If those policies are seldom followed, with clinical management more frequently denied or delayed, they become decoupled from clinical relevance when considering expense of a particular drug.

Third, expense calculations for bad outcomes associated with osteoporosis fractures were assumed to be normally distributed. However, those of us that have spent decades with population-wide clinical encounter data know that disease-specific expense is highly skewed. Specifically, the moments of the distribution that best characterize disease-specific expense distributions are first: skewness, second: variance, least: mean. The evidence used by ICER may be inadequate to characterize mean expense. They are grossly inadequate to characterize skewness.

For these reasons, ICER will be doing a serious disservice by making any recommendations based on the evidence cited. The only defensible recommendation is that further research is needed. The recommended research must include, at a minimum, head-to-head comparisons of Abaloparatide, Teriparatide, Romosozumab, and bisphosphonate. An example of one such study is the STRUCTURE trial, which compares Teriparatide to Romosozumab. Unfortunately, the results from this study are not yet fully published. We are not aware of any Abaloparatide vs. Teriparatide, Abaloparatide vs. Romosozumab, and all three vs. bisphosphonate.

Furthermore, ICER must develop criteria to specifically identify topics for which evidence is inadequate to make any recommendations. These criteria should include: (1) "Evidence Adequate," (2) "Evidence Marginal," and (3) "Evidence Inadequate." As a validation step, these proposed ICER criteria must find the current topic to be "Evidence Inadequate" as of June 1, 2017.

Sincerely,

Michael Graven, MD MSc MPH FRSPH
Vice President, Econometrics
Bendcare, LLC

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May 31, 2017

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: Draft Evidence Report on Osteoporosis

Dear ICER,

The Coalition of State Rheumatology Organizations, or CSRO, is an alliance of state or regional professional rheumatology societies formed in order to advocate for excellence in rheumatologic disease care and to ensure access to the highest quality care for the management of rheumatologic and musculoskeletal diseases. CSRO appreciates the opportunity to comment on policies outlined in the Institute for Clinical and Economic Review draft evidence report on Osteoporosis.

General Draft Report Concerns

In January, the Institute for Clinical and Economic Review (ICER) released an initial report on the coming assessment of comparative clinical effectiveness and value of three anabolic treatments for osteoporosis, one of which has been on the market for over 14 years (teriparatide), one that was only very recently approved (abaloparatide) and a medication that has not yet been approved (romosozumab). While the concept of comparative effectiveness is a rational approach for measuring value, the CSRO feels that this process must use comparisons with a more appropriate method.

ICER is comparing a group of bone-forming agents to a bisphosphonate – zoledronic acid, which is an antiresorptive agent. Its use can be limited by renal impairment which is common in the population that has osteoporosis. Additionally, in clinical practice these anabolic agents are primarily used to target the highest risk patient populations. The anti-resorptive drugs have a different mechanism of action, different onset of action and different lengths of treatment compared to anabolic therapies. The document states that these comparisons were valid as all of these drugs are approved for patients who are at high risk of fracture. Another drug which is also approved for treating patients at high risk of fracture, denosumab, was not included in this comparison for reasons that are not stated clearly. The CSRO also questions the definition of high risk of fracture as a T-score of -2.5 or lower AND a history of a fracture. In the clinical trials of these drugs, the definition of high risk of fracture does not include both of these criteria.

The CSRO also questions why morphometric fractures were not included as an outcome as morphometric fractures were the primary endpoints of all of the clinical trials for osteoporosis agents. Morphometric fractures are associated with increased morbidity including pulmonary disorders related to kyphosis, increased risk of subsequent fracture both vertebral and non-vertebral and increased fall risk, all of which have related costs that were not included in this model. Other costs that were not considered in this model include but are not limited to the cost of surgical repair of fractures, the cost of vertebral augmentation procedures, the cost of rehabilitation post-fracture, the cost of medications used to treat pain associated with fractures and the cost of treating comorbid conditions associated with these fractures such as pneumonia, pulmonary emboli, deep vein thromboses and bleeding post-hip fracture.

Comparative effectiveness and value evaluation should inform the medical and patient community in the best practices in making appropriate clinical decisions. The CSRO feels that the current ICER assessment should be amended to include the above information to better achieve its stated goals.

Respectfully,

A handwritten signature in black ink, appearing to read "Michael P. Jensen" with a stylized flourish at the end.

President
Coalition of State Rheumatology Organizations

May 31, 2017

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

Re: ICER Draft Evidence Report on “Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value”

Dear Dr. Pearson,

I appreciate the efforts of ICER to evaluate the effectiveness and value of anabolic therapy for osteoporosis. I have several comments for your consideration.

1. Clinical evidence

- a) **Limitations and uncertainties.** There is additional evidence on comparative effectiveness, not included in the ICER report, including a study showing superiority of teriparatide compared with risedronate in reducing vertebral fracture risk. Evidence is continuing to emerge for abaloparatide, a recently approved anabolic agent. Romosozumab, a sclerostin inhibitor, has been shown to have a dual-effect on bone remodeling, stimulating bone formation and inhibiting bone resorption, and therefore is not an anabolic agent in the same sense as teriparatide and abaloparatide. Recent developments regarding romosozumab may result in additional analyses of past studies and delayed FDA review. The fast moving pace of new data with these agents and many uncertainties suggest that it may be premature to reach any conclusions regarding comparative effectiveness.
- b) **Anabolic effects on bone structure.** It should also be noted that anabolic treatments for osteoporosis have beneficial effects on bone structure and bone strength that are not fully captured by bone density tests with DXA and cannot be measured by standard available clinical tools.
- c) **Order of treatment.** There are accumulating data that the sequence of treatment (e.g., anabolic before antiresorptive, anabolic after antiresorptive, anabolic combined with antiresorptive) may have important implications with clinical effectiveness.
- d) **Clinical trials vs. clinical practice.** Patients in clinical practice are often not the same as subjects who participated in pivotal fracture trials. Differences in comorbidities and preferences play an important role in the individualization of treatment decisions that should not be overly constrained by regulatory issues.

2. Long-term value for money

- a) **Uncertainties of pricing.** Teriparatide is likely to be available in generic form within the next several years and presumably have a different pricing structure than the current brand name product. The recently announced retail price of abaloparatide is considerably lower than brand name teriparatide. Expected pricing for romosozumab, an investigational agent, is unknown.
- b) **Cost-effectiveness modeling.** Any assessment of cost-effectiveness, if a valid assessment can be done at all, must consider pricing uncertainties of existing, new, and emerging

anabolic agents, the sequence of anabolic and antiresorptive therapies, and the use of antiresorptive agents other than zoledronic acid, such as denosumab.

3. Questions for deliberation

- a) The selection of zoledronic acid as the only choice for antiresorptive therapy does not reflect real-world clinical practice, where other agents, particularly denosumab, are often used in high risk patients.
- b) The definition of high risk solely according to T-score fails to include many high risk patients with T-scores better than -2.5.
- c) Comparison of “net health benefit” with a limited choice of options is an artificial constraint that is not representative of clinical practice, where many patients have been on multiple osteoporosis medications at different times and in combinations and sequences that could have variable effects on bone strength and fracture risk.

In summary, the numerous uncertainties and limitations of the data should lead the ICER report to be cautious in reaching conclusions of comparative effectiveness and cost-effectiveness. From what is known of the effects of anabolic agents on bone structure and bone strength, their use in proper sequence with highly effective antiresorptive therapy provides the best treatment option for appropriately selected high risk patients.

Respectfully,



E. Michael Lewiecki, MD
Director, New Mexico Clinical Research & Osteoporosis Center
Albuquerque, NM
Email mlewiecki@gmail.com



NATIONAL BONE HEALTH ALLIANCE
STRONG BONES AMERICA

May 31, 2017

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

RE: Institute for Clinical and Economic Review (ICER) Draft Evidence Report on treatments for osteoporosis and voting questions

Dear Dr. Pearson,

The National Bone Health Alliance (NBHA) appreciates the opportunity to provide input on the Institute for Clinical and Economic Review (ICER) Draft Evidence Report on treatments for osteoporosis and voting questions. NBHA, working closely with its' member and partner organizations, has engaged in a dialogue with ICER throughout this process and worked to share expertise and resources in an effort to ensure that patients with osteoporosis receive clinically appropriate treatments to manage this chronic disease.

The NBHA and its' members are concerned that complicated patients with osteoporosis, patients who are excluded from randomized clinical trials, are not adequately considered in the report. We understand ICER's intent is to have a process that is strongly based on the highest level of evidence; however, for patients at highest risk for fracture, using and even starting with an anabolic therapy may sometimes be the best choice and based on as yet unpublished clinical trial data, substantial observational data, and an understanding of bone physiology and the mechanisms of action of these drugs. We have detailed the evidence supporting our strong recommendation on this below.

Limited Data

- The report does not include more recent data such as The VERO study which was presented at WCO this year. VERO compared teriparatide to risedronate over two years with 680 patients per group in a double blind double dummy trial. Patients in the teriparatide arm had fewer vertebral fractures (5.4% vs 12%, $p < 0.001$) at two years. Equally important the difference was seen at one year as well (3.1% vs 6.0%, $p < 0.05$) showing the rapid onset of action of this anabolic therapy. Anabolics are more effective than antiresorptive therapy in terms of fracture reduction and have a more rapid onset. We understand that the VERO study has not yet been peer reviewed, but because there are so few studies, we believe it should be noted.

Timing of Report

- We understand the impetus to review anabolic therapies was the potential addition of two new anabolic agents in the marketplace Abaloparatide has just been approved, but review of

romosozumab is now delayed. It seems too early to be able to adequately assess the role of these anabolics in the treatment armamentarium.

- With the delay in the review of romosozumab, the discussion regarding this agent should be minimized. Furthermore, there are two large studies, VERO and ARCH, which when published, may help us better understand the role of anabolic agents.

Modeling

- The model compares one or two years of anabolic therapy to three years of an antiresorptive therapy (the HORIZON trial). It is not fair to compare therapies of different duration. One should compare equal duration of exposure, which would include one or two years exposure to an antiresorptive. It is understandable that there would be fewer hip fractures in a smaller trial of shorter duration. The registration trial for teriparatide was cut short because of safety concerns, although further surveillance has not demonstrated increased risk for osteosarcoma. Nonetheless, the lack of longer term studies with teriparatide make comparisons with anti-resorptive therapy studies that much more difficult.
- The authors of the report used nonvertebral fracture data to model for hip fracture reduction. Typically nonvertebral fracture reduction is lower as compared to hip fracture reduction with an osteoporosis therapy. A sensitivity analysis should be done to account for greater hip fracture reduction with an anabolic. We have both observational data in almost 9000 patients (Silverman presented at WCO 2017) and claims data (Burge) which suggest hip fracture reduction as high as 56% with an anabolic, teriparatide. *This becomes important since, of all fractures, incident hip fracture is associated with the greatest loss of health utility (define – death, independence, QOL).*
- The model assumes no “ramp up” for use of anabolics. Several studies have shown that prior treatment with an antiresorptive may blunt the BMD response of anabolics. Clinicians seeing a patient at very high risk for fracture might want to start with an anabolic first rather than an antiresorptive to realize the greatest bone density gains.
- The clinical trial data do not account for the differential effects on bone architecture seen with anabolic vs antiresorptive therapy. Some patients have poor bone quality as well as quantity at baseline and anabolics such as teriparatide have been shown to improve bone quality more than antiresorptive therapy, and this may then result in greater bone strength.
- There is a need for further risk stratification and sensitivity analyses.
- The basic model structure and assumptions used to complete the model-based cost-effectiveness analyses (CEA) should be more clearly and consistently stated. For a reviewer interested in the actual model structure and underpinnings, the report contains insufficient detail and could not possibly be reproduced from the information provided. Further information on model structure should be provided in appendices.
- An important area for further development relates to model validation. Model validation typically includes comparisons of modeled outcomes vs. epidemiological or other source data.
- The implementation of the fracture hierarchy as described in the draft report is problematic. As implemented at the time the draft was released the assumption effectively rendered the assertion that all tracked fractures were meaningless. This was discussed with the modeling team who says it is being/has been changed, but this requires further scrutiny and review of model validation results.

Transparency

- The document needs to help the reader understand why ICER chose to review these osteoporosis medications and explain all sources of ICER funding.

Voting Questions

- The voting questions are dichotomous and ask the panelists to vote on the net health benefit for postmenopausal women with osteoporosis as defined by a T score ≤ -2.5 and a fragility fracture, which is only a subset of the high risk population.
- The definition of high risk should be reexamined. We accept that patients with a fragility fracture of the hip or spine have osteoporosis independent of their bone density (Siris 2016). Studies have shown that almost half of patients with osteoporotic fracture have a BMD above -2.5, indicating that a T-score of ≤ -2.5 should not be the sole defining factor for risk. High risk may also be defined by clinical risk factors such as glucocorticoid exposure or patients with multiple fractures. Net Health Benefit ignores the urgency to treat in some patients. Patients who have had a prior fracture and those with multiple fractures have a substantially increased risk for future fracture, and the risk for subsequent fracture is greatest in the 2 years following the initial fracture. These patients may thus need the faster action of an anabolic, e.g. the 11.8% increase in lumbar spine BMD seen with teriparatide at just 18 mos.
- These voting questions ask panelists to vote only about a subset of the population at risk for further osteoporotic fracture
- The votes using the current voting questions should not be interpreted as providing any clinical guidance to clinicians or payers.

We would like to thank you for this opportunity to share our comments. The NBHA is eager to continue to work with ICER as it continues toward finalization of the Evidence Report on treatments for osteoporosis and voting questions. Please do not hesitate to contact Debbie Zeldow, our Senior Director of Clinical Programs, if you or your staff would like to discuss these issues in greater detail. She is reachable by phone at 703-647-3008 or via e-mail at Debbie.Zeldow@nbha.org

Sincerely,

Kenneth Saag, MD MSc and Robert Adler, MD
National Bone Health Alliance, Co-Chairs

United Rheumatology
315 Middle Country Road
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5/24/2017

Dr. Stephen Pearson
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

On behalf of United Rheumatology (UR), we are pleased to respond to the Draft Evidence Report for *Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value*. UR supports independent rheumatologists in their mission to strengthen the doctor-patient relationship and provide patient-centered, high quality, cost-effective care. We represent a growing network of 370 physician-members across 132 practices in 29 states. United Rheumatology's Medical Policy Committee has developed Clinical Practice Guidelines for multiple rheumatologic conditions, including Osteoporosis. These Guidelines are designed to be actionable standards for high quality, cost-effective treatment of patients and represent the collective understanding of experienced practicing rheumatologists throughout the country.

We commend ICER for its decision to evaluate the clinical effectiveness and value of treatments for osteoporosis. With osteoporotic fractures affecting one out of every two women over the age of 50 and one out of every 5 men in the United States, non-drug health care costs related to the care of patients with osteoporotic fractures was estimated to be \$17 billion in 2005 and will grow to \$25 billion by 2025. In this analysis, women account for 75% of the costs and 71% of the fractures.ⁱ In addition, escalating drug costs are a significant problem that limits access to treatment. Forteo (teriparatide) was approved by the FDA in November 2002. The wholesale price of the drug for 2 years of treatment in 2003 was \$13,440 (\$560/mo.) and by 2016 had climbed to \$61,248 (\$2552/mo.), a 356% price increase.ⁱⁱ Moreover, Medicare spend (Part B and Part D) for teriparatide, zoledronate and denosumab in 2015 totaled approximately \$1.6 billion.ⁱⁱⁱ

We applaud ICER's initiative to bring multiple stakeholders together, not in the interest of restricting access to critical and effective treatments, but to determine how to best address the challenge of rising drug costs. UR does, however, have fundamental concerns regarding ICER's analysis as well as specific questions regarding the modeling assumptions that were employed.

United Rheumatology disagrees with ICER's attempt to define patients at high risk for fracture as those who have had a prior fragility fracture AND have evidence of osteoporosis on a DXA study. Although alluded to in ICER's draft Evidence Report, this exact definition is not stated until the Questions for Deliberation (footnote 1): "High risk for fracture defined as the presence of a prior fragility fracture and a bone mineral density T-score of -2.5 or lower." From a practical standpoint, it is impossible to answer the 6 questions posed as none of the clinical trials used this definition as inclusion criteria for enrollment. As outlined in the list

below, all included studies offered alternate definitions for identifying patients at high risk for fracture.

- Patients in the pivotal teriparatide trial (Neer et al NEJM 2001) were enrolled if they had at least 1 prior vertebral body compression fracture; BMD was not an entry criteria. The mean lumbar spine T-score at baseline was -2.6, so a significant number of women had T-scores of better than -2.5.
- Patients enrolled in the ACTIVE trial (abaloparatide; Miller et al NEJM 2016) were included if the lumbar spine or femoral neck BMD was between -2.5 and -5.0. Fractures were not an entry criteria and in fact 37% of patients at baseline had no prior fractures.
- The FRAME trial (romosozumab; Cosman et al NEJM 2016) also enrolled based on BMD (here a T-score of between -2.5 and -3.5 in the total hip or femoral neck). Approximately 18% had 1 or more vertebral fractures and 21.8% had a non-vertebral fracture at baseline; so at least 60% did not have a baseline fragility fracture.
- The HORIZON trial (zoledronate; Black et al NEJM 2007) enrolled patients if they had femoral neck T-score of less than or equal to -2.5 with or without vertebral fracture OR if T-score was less than or equal to -1.5 then at least 2 mild vertebral fractures or at least one moderate vertebral fracture had to be present. 72 % of patients had BMD of < -2.5 and 63% of patients enrolled had evidence of a prior vertebral fracture.

No other organization has defined high risk for fracture as defined in ICER's Questions for deliberation. The FDA defines high risk for fracture as a "history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy," and currently applies this label to teriparatide, abaloparatide and denosumab. The American Association of Clinical Endocrinologists (AACE) defines patients at high risk for fracture as: 1) those with a prior fragility fracture; *or* 2) with low bone density and additional risk factor(s) including advanced age, frailty, glucocorticoids, very low T-scores, or increased fall risk.^{iv}

In addition to its lack of precedence, UR is concerned that the ICER definition, which requires not only a prior fragility fracture but also a BMD T-score of ≤ -2.5 , would unnecessarily restrict coverage of these drugs and exclude patients with fragility fracture(s) who have low bone mass/osteopenia on DXA study.

United Rheumatology disagrees with ICER's approach to compare anabolic therapies to the anti-resorptive drug zoledronate for the treatment of patients at high risk for osteoporotic fracture. Herein, we acknowledge a change in thinking from our earlier public comments that advocated studying *all osteoporosis drug therapies used in women at high risk for fracture* including denosumab (Prolia) and zoledronate as well as teriparatide (Forteo), abaloparatide (Tymlos) and Romosozumab (Evenity). Having also been involved with the ICER Evidence Report for Targeted Immune Modulators (TIMs) in the treatment of Rheumatoid Arthritis, which reviewed nine biologics and targeted synthetic DMARDs encompassing five distinct mechanisms of action in patients with moderate to severe rheumatoid arthritis, we

initially thought that a similar broad approach should be employed in osteoporosis. The critical difference in osteoporosis is that the structural effects on the target organ (bone) are profoundly different for anabolic as compared to anti-resorptive therapies whereas – in the joint – different TIMs could lead to similar effects on the inflamed synovium.

We would strongly encourage ICER and those viewing the public comments from stakeholders to once again review the elegant and masterfully written letter from Drs. Felicia Cosman and David Dempster in their roles as Co-Editor and Associate Editor respectively of Osteoporosis International dated December 23, 2016 and posted on the ICER website. The letter provides a cogent overview of: the head to head trials between anabolic and anti-resorptive therapies that favor anabolic drugs; the significant fracture benefit that occurs within 12 to 18 months of anabolic therapies; and the bone biopsy data that shows that anabolic drugs can restore microstructural integrity rather than simply preventing further structural deterioration. In addition, the importance of appropriate sequential therapy is underscored; treating with an anabolic followed by an anti-resorptive will lead to far greater improvements in BMD, especially in the hip, than simply treating patients with an anti-resorptive or using an anabolic drug after a course of anti-resorptive therapy.

As demonstrated, ICER should acknowledge the roles of anabolic and anti-resorptive drugs as complementary in sequential therapy and not as comparators or appropriate substitutes for one another, which could seriously limit the positive patient outcomes achieved through their treatment as such.

United Rheumatology disagrees with ICER’s refusal to acknowledge that radiographic vertebral fractures are an important clinical outcome. ICER instead assigns them to the “non-clinical outcomes” along with BMD and bone turnover markers. In earlier written communications with ICER regarding this topic, ICER incorrectly claims that “while radiographic fractures may be a risk factor for clinical fractures, they are asymptomatic events that are not treated”. In fact, radiographic vertebral fractures (or what has also been called morphometric vertebral fractures) are actively sought out by practicing clinicians and finding them can significantly alter treatment. Many current DXA machines include software that allows either single or dual energy imaging of the lateral spine; this procedure called VFA (Vertebral Fracture Assessment) is an essential element in the risk assessment, diagnosis and treatment.^v Depending on the age of the population studied, 16-45% of patients with low bone mass/osteopenia on DXA study have evidence of morphometric vertebral fractures. This finding changes the clinical diagnosis to osteoporosis and would lead to treatment where drug therapy otherwise may not have been indicated. In the spine, vertebral fractures can be graded mild/moderate/severe (Grade 1/2/3) and a spinal deformity index (SDI) can be calculated in which risk for future fragility fracture at any site increases with *increasing grade and number of vertebral fractures*.^{vi} The finding of several vertebral fractures and increasing grade of fracture will occasionally lead to use of an anabolic drug as compared to an anti-resorptive. Other studies have shown that morphometric vertebral fractures of the thoracic spine are clinically significant and impact pulmonary function studies.^{vii}

ICER acknowledges some of the limitations inherent in its modelling assumptions. UR agrees that the model has a number of flaws and omissions, including but not limited to the following:

- It does not address the common scenario of postmenopausal women who are already being treated for osteoporosis with an anti-resorptive.
- Adherence/persistence rates are inappropriately assumed to be 100% for all drugs studied. ICER states that there is “a lack of real world adherence data for newer anabolic agents (abaloparatide and romosozumab) and the impact of lower adherence on efficacy for all three anabolics”. Yet, adherence will be far better for drugs that are administered in the clinic (zoledronate, romosozumab and denosumab) compared to those self-administered at home, especially drugs requiring a daily injection. Adherence/persistence data is available for teriparatide in the United States (74% at 6 months and 57% at 12 months)^{viii} and there is no reason to assume it would be any different for abaloparatide. Moreover, the importance of the complexity of the treatment regimen on adherence and persistence is acknowledged by ICER in Section 5 “Other Benefits or Disadvantages”.
- In all the major trials of teriparatide, abaloparatide, romosozumab, zoledronate and denosumab, radiographic vertebral fractures are considered the primary outcome; yet, in the ICER cost-effectiveness model, cost/disutilities are only applied to clinical fractures.
- In the ICER model, quality of life never improves after a fracture.
- The model assumes that all patients are subsequently treated with yearly zoledronate for 6 years and that clinical fracture benefit appears immediately. No accommodation is made to include patients with renal insufficiency with creatinine clearance below 30-35.
- The baseline population had a “fracture risk...similar to that observed in the clinical trials of the anabolic agents”, but what that fracture risk *is* does not appear to be stated in the report. It appears that this fracture risk varies from what ICER defines as the high risk fracture patient with a prior fragility fracture *and* BMD T-score of lower than or equal to -2.5 as previously addressed within this response.

In addition to the concerns outlined above, UR makes the following suggestions related to the manuscript itself which are listed here. ICER should:

- Correct the inexplicable dismissal of denosumab (Prolia), which is inaccurately grouped with calcitonin, raloxifene and estrogen as alternate anti-resorptives that “are not considered first-line therapies because of side effects or less evidence of efficacy.”
- Include some discussion related to the relevance of grading of vertebral fractures since Table 2 introduces the grading criteria.
- Update its reference to abaloparatide (Tymlos) on page 8, within the first paragraph, to reflect that it is now approved by the FDA.
- Correct the error within Table 8; the 5th row states that romosozumab is modeled based on trial data of two years; in actuality, the trial with active drug was for 12 months followed by 12 months of denosumab. This is correctly stated on page 34 under Treatment Strategies paragraph 2 and should be corrected here.
- Correct the error within Table 13, where zoledronic acid is listed as 5mg but strength in column 2 states 4mg/5ml. Zometa, zoledronate for oncology use, is available as a 4 mg dose.

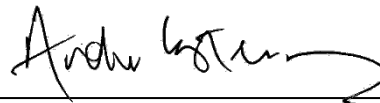
In the section titled “Other Benefits and Disadvantages” there is no discussion of how a patient’s health insurance coverage will affect access to these drugs. A significant number of Medicare patients do not have either a low-income subsidy or supplemental health benefit that would allow them to afford the cost of Part D drugs such as teriparatide and abaloparatide purchased at an outpatient pharmacy. In contrast, since zoledronate, romosozumab and denosumab are administered in-office, they would be covered under Part B (medical benefit) and thus would be far more affordable.

Finally, an FDA decision on romosozumab/Evenity was initially expected on 7/19/2017 but Amgen just announced on 5/20/2017 that they do not expect FDA approval this year. The delay is related to a new cardiovascular safety signal in the ARCH study which compared 12 months of romosozumab followed by 12 months of Fosamax with Fosamax alone in post-menopausal women with osteoporosis at high risk for fracture. The incidence of positively adjudicated cardiovascular serious adverse events (SAEs) at 12 months was 1.9% in the Fosamax arm and 2.5% in the romosozumab arm (a 32% increase).^{ix} In contrast, the FRAME study which had been submitted to the FDA did not report an imbalance in cardiovascular SAEs when romosozumab for 12 months was compared with placebo for 12 mos. with both followed by denosumab for 12 mos. The ICER model currently does not assume any serious adverse events for the anabolic therapies. It is too soon to know whether this will need to be modified.

Sincerely,



Max Hamburger, MD FACP FACR
President; Medical Policy Committee



Andrew Laster, MD FACR
Board of Advisors; Medical Policy Committee

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ⁱⁱⁱ CMS 2015 Medicare Drug Spending Dashboard. Retrieved from: <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/2015Medicare.html>

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^v Laster AJ, Lewiecki EM. “Vertebral Fracture Assessment by Dual Energy X-ray Absorptiometry: Insurance Coverage Issues in the United States. A White Paper of the ISCD.” *Journal of Clinical Densitometry* 2007. 10:227-238

^{vi} Siris ES, Genant HK, Laster AJ et al. Enhanced prediction of fracture risk combining vertebral fracture status and BMD. *Osteoporosis Int* 2007

^{vii} Krege JH, Kendler D, Krohn K et al. Relationship Between Vertebral Fracture Burden, Height Loss and Pulmonary Function in Postmenopausal Women with Osteoporosis. *Journal of Clinical Densitometry*.2015.18:761-70

^{viii} Foster SA, Foley KA, Meadows ES et al. Adherence and Persistence with Teriparatide Among Patients with Commercial, Medicare and Medicaid Insurance. *Osteoporosis International* 2011. 22(2): 551-557

^{ix} Amgen Evenity Approval Derailed on Cardiovascular Side Effect. *Zacks Equity Research*. May 22 2017.

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