

FDA Workshop: “Osteoporosis Drug Development: Moving Forward”

Testimony by Douglas P. Kiel, M.D., M.P.H., ASBMR President The Need for Surrogate Endpoints for Fracture November 4, 2015

Good afternoon. My name is Douglas Kiel. I am President of the American Society for Bone and Mineral Research, or ASBMR. I am a Professor of Medicine at Harvard Medical School and Director of the Musculoskeletal Research Center and Senior Scientist for the Institute for Aging Research at Hebrew SeniorLife. I would like to thank the FDA, the expert panelists and the audience for the privilege of engaging with you to confront challenging issues in osteoporosis drug development.

As a physician scientist who treats patients with osteoporosis, my words today reflect the collective thoughts of ASBMR’s members. Nearly 4000 preeminent physicians and biomedical scientist members make ASBMR the world’s largest, most respected society on bone, mineral and musculoskeletal research.

Within fifteen years, approximately one in five US residents will be over 65 years old. In 2010, osteoporosis – which causes fractures, musculoskeletal decline and loss of independence – was one of the 10 most costly chronic conditions to Medicare. Currently, 10.2 million Americans are estimated to have osteoporosis and 43.4 million more have low bone mass, increasing their risk of fragility fracture. In the US there are 2 million osteoporotic fractures per year; during my 10 minute presentation, 200 osteoporotic fractures will have occurred worldwide. How will we meet the challenge of preserving skeletal health and independence in our rapidly aging population with the limitations of the current osteoporosis treatments?

While the currently available osteoporosis medications reduce the risk of fractures, no current agent is able to fully restore skeletal integrity in patients with established disease. Moving forward, we believe that it is crucial to achieve better clinical outcomes for our patients. To realize this goal, we need new, more powerful, treatments that can safely be given long-term.

Unfortunately, despite the enormous need, the osteoporosis drug pipeline is severely diminished. Ironically, this reduction in new drug development is occurring during a period of unprecedented scientific advances in bone biology, including the identification of promising new drug targets. The impending drought in osteoporosis drug development is caused, in large part, by current clinical trial requirements to demonstrate anti-fracture efficacy to achieve regulatory approval. These trials severely restrict drug development efforts, requiring prohibitively large study populations of at risk individuals who are followed sufficiently long to demonstrate fracture efficacy.

Identifying surrogate endpoints for fracture for use in clinical trials will revive the osteoporosis drug pipeline, paving the way for new treatments for patients with osteoporosis.

The FDA Safety and Innovation Act encourages “the expedited development and review of innovative new medicines intended to address unmet medical needs for serious or life-threatening disease or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints.” In contrast to the bone field, many other therapeutic areas employ surrogate endpoints that serve to expedite drug development. In fact, the pivotal trial of nearly half of all approved therapeutic agents and indications from 2005-2012 used a surrogate outcome.

Although osteoporosis is a life-threatening disease, current osteoporosis drug development does not follow the guidance of the Act or the precedent set by other therapeutic areas to use surrogate endpoints. Instead, under current FDA requirements, the development and review process is slow, requiring large, lengthy phase 3 trials with a fracture endpoint. The current regulations date back 30 years and are due, to a large extent, to the unexpected observations of the sodium fluoride trials. Fluoride treatment increased bone density while simultaneously increasing fracture rates, calling into question the use of surrogate endpoints to predict anti-fracture efficacy. What is different today is that new drugs must go through a pre-clinical phase with mechanical testing in animals. If this standard were used during fluoride’s development, the reduction in bone strength would have been identified before initiating clinical trials.

The past does not have to define the future. Over the past two decades, we have greatly increased our understanding of the diverse factors that contribute to bone quality and strength. Additionally, researchers have made vast improvements in the way bone strength is assessed, including the development of sophisticated *in vivo* imaging, biomechanical testing and finite element modeling. Developing and validating surrogate endpoints such as these for use in clinical trials will dramatically accelerate patient access to new drugs and ultimately preserve independence and save lives.

Several projects are underway to collate and analyze existing massive clinical datasets, including the FNIH Biomarkers Consortium Bone Quality Project, of which ASBMR is a member. This in-depth analysis of pooled bone mineral density measurements, advanced imaging assessments and biochemical data from numerous clinical trials aims to identify the best biomarker candidate, or combination of biomarkers, to predict clinical outcomes. Combined with continued research in the field, the recommendation of a high quality surrogate will be evidence-based and supported by substantial data.

As our understanding of specific biomarkers and imaging techniques evolves, the continuing need for FDA guidance is critical. We request that the FDA work with the bone community within the framework of the Biomarkers Qualification Program to develop the profile of an acceptable surrogate marker for fracture in phase 3 osteoporosis drug trials. This is a top priority for ASBMR. We offer our support and will enthusiastically work with stakeholders to identify models for surrogates that will meet FDA requirements.

As we stand here discussing the future, we can’t forget that some changes can be implemented now to expedite and broaden patient access to safe and effective therapies.

First, we must reconsider phase 3 clinical trial designs. We encourage the FDA to consider allowing the sponsor to determine study duration and the freedom to choose a placebo and/or active control in phase 3 clinical trials. These choices provide the necessary flexibility for sponsors to execute clinical trials in countries with varying regulations.

Second, we support simplifying the indication for treatment so that it does not rely on vague disease severity tiers. We favor treatment indications that are simply based on an individual being at increased risk of fracture. The current use of treatment tiers is not evidence-based and prevents patient access to effective medications.

Like many ASBMR members I represent, I see first-hand the ravages of osteoporosis – pain, fractures, loss of mobility and independence, and diminished quality of life. Our current and future patients with osteoporosis and fractures deserve better.

Our current armamentarium of osteoporosis treatments is not good enough. We need a broader range of agents that restore skeletal integrity and can be given safely long-term. Thus, expediting review of new drugs is even more important. To achieve this, we must start now. As considerable work is already underway, we urge the FDA to provide concrete guidance on validating surrogate endpoints and to consider the other short term strategies we propose.

Each of us must contribute our expertise and work together for the benefit of those who currently and will suffer from osteoporosis. With collaboration, hard work and communication, we can achieve more than the sum of our parts. ASBMR eagerly anticipates contributing to and facilitating continued dialogue on these challenging issues. Thank you for the opportunity to participate in this discussion.