FDA PUBLIC WORKSHOP
OSTEOPOROSIS DRUG DEVELOPMENT: MOVING FORWARD
November 4, 2015

I. Background

Osteoporosis, a disease characterized by an increased risk for fracture, is diagnosed using bone mineral density (BMD) or, in some cases, by the presence of a fragility fracture. The intent of treating osteoporosis is to prevent fracture. The hurdles of osteoporosis drug development are well-recognized, including the large trial size necessary to demonstrate fracture risk reduction. The history of osteoporosis drug development is summarized in the article *The Food and Drug Administration's Osteoporosis Guidance Document: Past, Present and Future* (Colman, 2003), which is included for your reference.

This workshop is being convened to discuss issues related to osteoporosis drug development. The workshop is divided into three sessions. In the first morning session, we will discuss the appropriate target populations for osteoporosis treatment and prevention and the two existing indication statements for osteoporosis treatment. The second morning session will focus on osteoporosis clinical trial design issues including trial duration and the acceptability of active controlled trials intended to demonstrate noninferiority with regard to fracture outcomes. The FDA is planning to write a draft guidance on drug development for osteoporosis and will take into consideration the discussions from these two sessions. The objective of the afternoon session is to begin a discussion on the use of endpoints other than fracture for registration of therapies for osteoporosis. This session will include a presentation on biomarker qualification.

The questions for discussion are included in each session section below. There are no voting questions. Our goal is to have a robust discussion of the issues. We have assembled a panel that encompasses different perspectives and we look forward to the discussions during each session.

II. Osteoporosis Treatment and Prevention: Indication Language and Target Population

The first morning session will focus on the appropriate osteoporosis treatment and prevention populations, the current osteoporosis indications and whether there should be changes to the indication language.

Currently, most expert groups recommend that all women aged 65 or older have BMD testing to screen for osteoporosis. Several expert groups also recommend screening for osteoporosis in women who have risk factors for osteoporosis or have had a prior

fragility fracture. There are no recommendations for screening all postmenopausal women under age 65.

Recommendations for pharmacologic treatment for osteoporosis include patients who meet the BMD criteria for osteoporosis (T-score of -2.5 or less) as measured by dual x-ray absorptiometry (DXA), patients with a hip or vertebral fragility fracture, or patients with low bone mass (T-score between -1.0 and -2.5) who have a 10-year probability of ≥ 3 percent for a hip fracture or ≥ 20% for a major osteoporotic fracture using the FRAX risk model. Many patients that should be treated for osteoporosis are not receiving therapy even in the setting of an osteoporotic fracture.

From a regulatory perspective, the indication for treatment of postmenopausal osteoporosis encompasses both primary and secondary fracture prevention in patients with osteoporosis. The target population in the osteoporosis clinical fracture trials of approved agents has evolved over time. While the mean age of enrollees has remained relatively constant at approximately 70 years old, the percentage of subjects with baseline fracture has markedly decreased. Seventy percent to 100% of enrolled subjects had a fracture at baseline in fracture outcomes trials initiated prior to 2000. Since 2000, the percentage of subjects with a baseline prevalent vertebral fracture has decreased to 63% of enrolled subjects with prevalent vertebral fracture in a trial initiated in 2002, and 24% of enrolled subjects with prevalent vertebral fracture in a trial initiated in 2004. Therefore, more recent study populations predominantly reflect patients with osteoporosis who are receiving treatment for primary fracture prevention. We recognize that this is occurring because it is no longer ethical to enroll women at higher risk of fracture into placebo-controlled trials given the duration of the trials and available therapies. We believe that it is acceptable to extrapolate fracture benefit seen in a lower risk osteoporosis population to a higher risk population.

Since 1995, the treatment of osteoporosis indication statement has generally been “treatment of osteoporosis in postmenopausal women.” Since 2002, the FDA has used a more restrictive indication: “treatment of postmenopausal women with osteoporosis at high risk of fracture” for those therapies that have significant safety concerns requiring further assessment in large, postmarketing clinical studies. The labels for these therapies define “high risk of fracture” as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. The intent of this more restrictive indication is to target those patients who are most likely to derive benefit that outweighs the significant risks. We believe that the distinction between these two indications is important for prescribers. However, we also understand that it presents confusion in light of the European Medicines Agency (EMA) indication for all osteoporosis treatments: “treatment of osteoporosis in postmenopausal women at increased risk of fracture”. We would like to hear panel members’ opinions and discussion about the treatment of osteoporosis indications.

Discussion Questions:

The FDA currently uses two different indications for the treatment of osteoporosis, a more general indication for the treatment of postmenopausal osteoporosis, and a more restrictive indication for the treatment of postmenopausal osteoporosis in patients at high risk of fracture.

a) Does the indication statement impact your decision on which therapy to prescribe for a patient?

b) Does the current approach to the indication statement help you differentiate the risks and benefits of a particular product?

c) What recommendations do you have regarding the indication statements for treatment of postmenopausal osteoporosis?

For the indication for prevention of postmenopausal osteoporosis, earlier clinical trials enrolled postmenopausal women without regard to BMD at study entry. The inclusion criteria have evolved over time to postmenopausal women with low bone mass defined as a lumbar spine BMD T-score of -1.0 to -2.5. However, this target population for the prevention of osteoporosis indication no longer aligns with current treatment recommendations unless other risk factors for fracture are present and the 10-year probability of fracture is sufficiently high using the FRAX risk model. This leads to overlap with the treatment of osteoporosis indication. In addition, we recognize that prolonged treatment with many of the therapies indicated for prevention of osteoporosis is associated with rare but significant side effects. For these reasons, we conclude that the nonspecific prevention of osteoporosis indication should be refined to reflect a more targeted population for whom treatment is advised.

Discussion Questions:

a) Based on the known long-term safety concerns associated with many osteoporosis therapies, what is the appropriate target population for a prevention of osteoporosis indication?

b) Do you have any other recommendations regarding the prevention of postmenopausal osteoporosis indication?

III. Osteoporosis Clinical Trial Design

The second morning session will focus on clinical trial design issues pertaining to fracture trials. For product registration, morphometric vertebral fracture is the primary endpoint of interest. The FDA does not require demonstration of fracture reduction efficacy at other nonvertebral sites or at the hip, although this might be commercially preferable.

The first issue is fracture trial duration. Since the 1994 guidance, the FDA has required 3 years of data demonstrating fracture reduction efficacy. This was mainly driven by the loss of efficacy noted in the third year of the etidronate fracture trials raising questions about durability of effect. As outlined in the table below, we have evaluated, where possible, the primary endpoint data at 1 year, 2 years, and 3 years in the approved osteoporosis trials and have concluded that 2 years of fracture data would be sufficient for a fracture registration trial. Two years of exposure data will also allow adequate assessment of safety although we recognize that it will not allow assessment of potential longer term safety concerns.

Reduction in New Morphometric Vertebral Fracture Over Time During Clinical Trials of Approved Osteoporosis Therapies

		12 Months		24 Months		36 Months	
		ARR	RRR	ARR	RRR	ARR	RRR
Alendronate	US/MN pooled					3.2	48%
	FIT, baseline fx			7.2	62%	7.1	47%
Raloxifene	baseline fx					6.1	30%
	no baseline fx					2.4	55%
Risedronate	VERT MN	7.7	61%	13.1	59%	10.9	49%
	VERT NA	4.0	65%	5.9	55%	5.0	41%
Teriparatide **				9.3	65%		
Ibandronate						4.9	52%
Zoledronic Acid		2.2	60%	5.5	71%	7.6	70%
Denosumab		1.4	61%	3.5	71%	4.8	68%

MN = Multinational
fx = fracture
ARR = Absolute Risk Reduction compared to placebo
RRR = Relative Risk Reduction compared to placebo
** 19 month data

Discussion Questions:

a) Do you agree that a clinical fracture trial of two years duration will provide sufficient exposure to adequately characterize treatment effect and the durability of effect, as well as safety, of an investigational osteoporosis therapy?

b) Do you have any other recommendations regarding fracture trial duration?

The second issue for discussion is the comparator arm for fracture trials. FDA is open to use of an active-control rather than placebo in required fracture trials. Such trials could be conducted as superiority trials or as noninferiority trials. However, there are

important considerations and challenges with noninferiority trials, as discussed in FDA's draft *Guidance for Industry: Non-Inferiority Clinical Trials,* which is included for your reference.

The FDA has a long history of accepting noninferiority trials using a BMD primary endpoint for new dosing regimens of already approved osteoporosis products. Once fracture efficacy has been demonstrated in a trial that also includes BMD endpoints, it is acceptable to use noninferiority of BMD as the endpoint for a new dose regimen compared to the dose regimen used in the fracture trial.

For fracture trials utilizing noninferiority, it will be important to use a comparator with a reliable and reproducible treatment effect. With the exception of alendronate and risedronate, all other approved osteoporosis treatments each have fracture efficacy data from only single trials. Once an active comparator has been identified, determination of the noninferiority margin is vital. It is important to understand how much loss of the treatment effect of the active comparator control is clinically acceptable.

Discussion Questions:

a) Is a noninferiority fracture trial utilizing an appropriate well-characterized comparator acceptable? What agents would you find acceptable for use as an active comparator for osteoporosis fracture trials?

b) What would you consider to be the largest clinically acceptable non-inferiority margin or loss of effect for fracture noninferiority?

c) What population would you enroll in a non-inferiority fracture trial, given that these trials would not randomize patients to placebo?

d) Do you have any other recommendations regarding the design of Phase 3 fracture trials?

IV. The Future of Osteoporosis Trials

The afternoon session will focus on developing endpoints other than fracture for osteoporosis registration trials. The FDA has required evidence of fracture reduction efficacy since 1994. This requirement was instituted when it became clear that change in BMD is an imperfect surrogate because it did not always predict fracture reduction outcomes. Studies of fluoride and etidronate that lead to this decision are well known. Additionally, the case of a dosing regimen for intravenous ibandronate that increased BMD but did not reduce fracture outcomes, also reinforced the concern.

While the FDA has reservations regarding use of BMD alone as a surrogate for fracture outcomes, there is opportunity for development of other endpoints or models for

predicting fracture outcome. This session will include presentations related to ongoing investigations in the topic of biomarker and modeling development.

The FDA's approach to qualification of biomarkers for drug development has evolved and will be a topic of the first presentation for the afternoon session. The FDA's approach to biomarker qualification is included in the attached articles: *Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization* (Amur, 2015) and the *Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools*, which are included for your reference.

To facilitate the discussion, the article *Bone Quality: A Perspective from the Food and Drug Administration* (Kehoe, 2006) is also included for your reference.

Discussion Questions:

a) What is your opinion regarding the use of endpoints other than fracture for registration of therapies to treat osteoporosis?

b) Do you have any other recommendations regarding potential endpoints other than fracture, biomarker qualification, or pharmacometric modeling?