Endocrinologic and Metabolic Drugs Advisory Committee
Center for Drug Evaluation and Research
Food and Drug Administration
Clinical Trials for New Osteoporosis Treatments
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statement of
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My name is Amy Allina. I am the Program & Policy Director of the National Women's Health Network. The Network is a non-profit organization that advocates for national policies that protect and promote all women's health. We also provide evidence-based, independent information to empower women to make fully informed health decisions. The Network does not accept financial support from pharmaceutical or medical device companies and is supported by a national membership of 8,000 individuals and 300 organizations.

We're here representing concerns shared not just by our members but also by millions of women who, particularly in the wake of the news this summer about the Women's Health Initiative results, are struggling with questions about the safety, effectiveness and need for drugs prescribed at menopause. While the topic of this meeting is clinical trials for new osteoporosis treatments, it touches on issues that go far beyond clinical trials and affect the way that women are educated about bone health, screened for bone density loss, counseled on prevention strategies and finally treated for osteoporosis. We recognize that this committee and the FDA do not control all those aspects of women's health care, but we address them in our comments because the way that clinical trials for osteoporosis drugs, particularly prevention trials, are designed will have consequences for women's health education and care.

In the 1980s and earlier, we were among the women's health advocates who agreed that the problem of bone fractures and their effect on elderly women's quality of life was being overlooked by the medical community and needed to be addressed. Today, the pendulum has swung to another extreme for those women with access to health care and insurance coverage. Now we believe it's the case that women who are in the health care system are commonly over-screened, over-diagnosed and over-treated for problems relating to their bones. At the same time, it's still true that there are women who would benefit from screening and treatment who don't get the care they need as a result of economic and other barriers to accessing health services.

Bone density screening has become a rite of passage for women approaching and entering menopause. This means that women are being screened in their forties and fifties which we believe is far too early to use a test that has not been shown to be a reliable predictor of fractures which typically occur 20-30 years later. But why is this a problem? What's the harm in taking a measure of bone density? Many people assume that osteoporosis screening must be a good

thing. They don't recognize its limitations or how it plays into the medicalization of menopause.

The problem is that over screening leads to over treatment. Just as many of you who see patients must, we hear story after story of women who have been told that they have the so-called disease of osteopoenia or that they need a prescription for their "borderline osteopoenia." Once diagnosed like this, women may be less likely to do exactly the thing that could help ensure that they maintain their "borderline" bone health – staying physically active. And many of these women are given prescriptions and told that they must take drugs to prevent their osteopoenia from developing into osteoporosis and leading to bone fractures. Some of them may need help from a drug to prevent serious bone loss and debilitating fractures. But many of them don't, and the bone density test is not a sufficiently reliable predictor of fractures to support this use of it.

The experience of hormone replacement therapy should serve as a warning example of a drug that was prescribed to millions of women based on false assumptions about both unproven benefits and inadequately tested safety.

So, how does this relate to the discussion issues that you must address? Clinical trial design doesn't control clinical practice, but it has a direct effect on it. As you think about the answers to the questions that FDA staff has posed to you, we urge you to put them in the context of how these clinical trials of new osteoporosis treatments will affect the way the drugs tested will be put to use in clinical practice and the way they will, therefore, affect women's lives.

Efficacy

1. When is bone mineral density an adequate primary endpoint?

Our answer to this question is never. We recognize that this puts us outside the mainstream of discussion, but we are not alone in questioning the value of bone mineral density measures. The 2000 National Institutes of Health consensus report on osteoporosis produced raised questions about the accuracy of bone mineral density testing and recommended that more comprehensive ways of assessing risk for fracture should be studied. Because of this, we believe the design of the typical prevention trial using bone mineral density as an endpoint is flawed.

2. What duration of study is appropriate for assessment of effectiveness?

The necessary duration of study depends on the age of the trial participants. If study durations are going to continue to fall in the 2-3 year range, or certainly if they are going to be shortened, we believe that prevention trials should not be conducted on women younger than 65 unless those women are at particularly high risk for bone fractures because of the early removal of ovaries or long-term steroid use. It isn't possible to determine in the short-term of a 2-3 year trial whether a drug has effectively prevented bone fracture in a younger woman who has not yet reached the age at which she is most likely to experience bone fractures.

3. When is the use of a placebo or an active control appropriate?

The new understanding of the risks posed by hormone therapy significantly change the terms for discussing this issue. While the Women's Health Initiative showed us that estrogen plus

progestin is highly effective for osteoporosis and will likely show the same for estrogen alone, it also demonstrated that the combined hormone regimen poses serious health risks which outweigh its benefits for healthy women. Therefore, it's no longer possible to hold HRT out to be the gold standard for comparison in a trial of a new osteoporosis drug.

In prevention trials, we believe it is still appropriate to use a placebo control. In treatment trials, however, where participants have experienced a fracture prior to beginning the trial, an active control is both ethical and appropriate. Moreover, it is desirable because it may provide more valuable and useful results by showing whether a new drug offers a benefit over existing options in terms of either efficacy or safety. This response holds true from the perspective of considering safety as well as efficacy.

Safety

1. Can the incidence of osteoporotic fractures be used as a safety rather than an efficacy endpoint?

Osteoporotic fractures should be used as both a safety and an efficacy endpoint in both prevention and treatment trials. The intermediate endpoint of bone mineral density is not an adequate measure of a drug's effectiveness or its safety.

3. What duration of study is appropriate for the assessment of safety?

While we recognize that it is not practical to require sponsors to conduct trials that last 10 or more years, women who are prescribed drugs for osteoporosis are likely to be taking them for decades. Therefore, it is necessary to gather data on the safety of such long-term use. FDA should recognize this need by making long-term follow -up studies on these products a condition of approval and by putting in place active systems for monitoring adverse reactions to the drugs.

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