My name is Dr. Mary Carol Jennings and I speak today on behalf of the National Research Center for Women & Families.

Our nonprofit research center's medical and public health experts analyze and review complicated research findings to provide objective, understandable information to patients, providers, and policy makers. We do not accept funding from pharmaceutical companies so I have no conflicts of interest.

I trained in obstetrics and gynecology at Boston University Medical Center, and our Center is dedicated to supporting the use of safe and effective treatments for osteoporosis. I also want to mention that our Center's president serves on the Board of Directors of the Alliance for a Stronger FDA, which is a coalition of public health, patient, and consumer nonprofits AND pharmaceutical companies, working together to increase the financial and scientific resources available to the FDA.

I am here today because we believe in the important work of the FDA and we know that these Advisory Committee meetings can be very challenging as you review complicated data, as you are asked to do today.

The FDA has asked you to consider whether the data support the continued sale of calcitonin salmon for post-menopausal women, and if the FDA should require fracture efficacy data for new products

I will answer the second question first. Since 1994, products for postmenopausal osteoporosis have been required to significantly reduce fractures over 3 years of treatment (p7). That same standard should be applied to calcitonin.

Until now, calcitonin products have been approved on the basis of the "surrogate" endpoints of bone mineral density. BMD is used to diagnose osteoporosis, but it has long been recognized that it can't predict the risk of a bone fracture by itself (p6).

When Novartis finally completed its promised phase IV trial for nasal Miacalcin – CT320, or the PROOF trial, it appeared to show a marginally significant reduction in new vertebral fractures with a 200 IU dosage (p53) The P value was .03, but given the large number of comparisons (varying dosage levels, fracture sites, and bone mineral density sites), a P level of at least .01 would be more appropriate.

There was no significant reduction in non-vertebral fractures, which was expected since such fractures are relatively rare and the sample was not large.

At the same time, this study showed a substantial trend for cancer risk : 8.6% in calcitonin salmon patients compared to 5.1% in the placebo patients.

The **lack of a dose response was surprising: 200 IU marginally reduced vertebral fractures but neither 100 nor 400 IU reduced** vertebral fractures. These results for different dosages are not biologically plausible, which suggests that the marginal effect of 200 IU happened by chance. Moreover, the 400 IU dose resulted in lumbar spine BMD effects at least as favorable as 200 IU, so if BMD works as a surrogate for fractures, the higher dose should also have reduced fractures. It didn't.

In A2302, the company's (Novartis) much larger three-year study, oral CS **did NOT** significantly reduce vertebral fractures or other fractures (in women with PMO)

In addition to being much larger, this study enrolled a more geographically and racially diverse population. And the women had a much lower baseline prevalence of vertebral fractures (22% vs. 79%) and therefore a lower fracture risk.

This study also showed small increases in lumbar spine BMD (1.0-1.5%) compared to placebo, and like the other study, this increase occurred in the first year of treatment, with little change after that. So, both studies showed increase in BMD but only one showed a decrease in fractures.

So, to answer the first question: we urge you to vote NO: the data do NOT support the continued marketing of calcitonin for postmenopausal osteoporosis.

I'd like to go a step further in this discussion. We believe that the use of x-rays to detect vertebral fractures is not a clinically relevant outcome measure for an osteoporosis drug. Most women take these drugs to prevent hip fractures – that is the major concern for osteoporosis. Women are not aware that the osteoporosis drugs are not proven to significantly reduce hip fractures.

Vertebral fractures found on x-rays do not have symptoms, and the clinical significance of these fractures – and of reducing these fractures – is unknown. The FDA has recently emphasized its interest in patient-centered outcome research. If the FDA wants to focus on outcomes that are meaningful to patients, they should require outcome measures that clearly benefit patients. BMD does not. And, there is no clear evidence that non-symptomatic vertebral fractures do either.

What about SAFETY?
The studies presented are not ideally designed to measure safety in humans, and especially not in the women who are most likely to take these medications. However, as shown most clearly in the Forest plot and table on page 27 and page 29 of the FDA memo that was provided to you, **it is clear that most of the studies of either the nasal or the oral forms (p27, 29) of calcitonin demonstrate a higher cancer risk compared to**

placebo. These meta analyses showed a non-significant trend of higher rates of cancer for patients taking calcitonin compared to placebo.
These studies are not conclusive but they certainly are cause for concern. We agree with the FDA that the potential for cancer risk for calcitonin "cannot be ignored."

Conclusions:
Last year (2012) the European Medicines Agency found that the "limited efficacy" of calcitonin does not outweigh the risks, and recommended withdrawing the nasal spray for osteoporosis (p11). We agree.

We believe that neither the oral nor the nasal products are proven effective to reduce fractures and that the potential risk of cancer indicates they may harm more patients than they help.