

# MEMORANDUM

To: Division of Endocrine and Metabolic Drug Products  
FDA Center for Drug Evaluation and Research  
Attn: Randy Hedin (HFD-510)  
C/O Division of Dockets Management (HFA-305)

From: Henry Bone, M.D.

Date: April 12, 2004

Re: Comments on draft guidance "Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis" (1994)

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Over the years since the current draft of the guidance was issued, a great deal of experience has demonstrated that its principles remain sound, and fundamental changes are neither necessary nor appropriate. I was involved in the development of the current guidance as a consultant to FDA, and have been involved in its implementation as an investigator, a participant in discussions with sponsors, as an advisor to FDA, and in discussions with CPMP members and others concerned with the development of drugs for osteoporosis and related disorders. Taking into account this experience and perspective, I have several comments on the guidance, including but not limited to the questions specifically posed in the request for comments:

1. As was extensively discussed in our EMDAC meeting in September 2002, placebo-controlled fracture-endpoint trials are appropriate and acceptable when they enroll participants who have not had recent or multiple fractures, in whom the diagnosis of osteoporosis is established by bone densitometry. This assumes that calcium and vitamin D are background therapy for all subjects, so that the placebo is control for the test drug, but none of the subjects are truly deprived of all treatment. Of course, prospective subjects must be informed as to the risks and potential benefits of study participation and alternatives. Individuals with higher estimated fracture risk associated with recent or multiple fractures would be acceptable for placebo controlled fracture-endpoint trials if they have contraindications to, or refuse, approved therapy. Individuals found to have a single, relatively minor compression deformity that is not acute are probably closer to the first category (eligible).
2. The standard observation period for the main phase III trials should remain three years, regardless of the duration of investigational drug exposure, especially for drugs in novel classes or with novel mechanisms of action. This gives an opportunity to observe the effects of treatment after the "remodeling transient" effect. The importance of the third year was well illustrated by the experience with etidronate. However, there may be circumstances in which the three years could reasonably be accelerated. For example, in the case of true estrogens, the main issue is the selection of the lowest effective dosage. For this purpose, a two-year observation period should be adequate, although there might well be a need for longer-term safety data. For well characterized, thoroughly studied drugs from well-established classes, two years of observation might be adequate for the primary analysis for the NDA submission, with submission of the third year data for review prior to actual approval.
3. One of the major factors affecting trial size is the need for data about antifracture efficacy at sites other than the vertebrae. Separate trials should not be required to establish anti-fracture efficacy at different anatomical sites. For example, the spine, all non-vertebral sites

taken together, and the femur should be evaluable in a single trial, provided that appropriate statistical measures are employed.

If anti-fracture efficacy is established for the spine, it should not be necessary to employ two-tailed statistical tests for other categories of fractures, unless there is a specific reason to do so (such as an observed loss of bone density at femoral sites despite an increase in the spine). Furthermore, once anti-fracture efficacy is established for vertebral and non-vertebral fractures, the statistical standard for specific anatomical sites, e.g., the proximal femur, should be less stringent, taking into account the fact that the information is not being considered in isolation. For such confirmatory analyses, a confidence level of 90% should generally be adequate.

4. Anti-fracture efficacy data can usually be extrapolated from low-risk populations to higher-risk populations. Effective drugs for postmenopausal osteoporosis have consistently produced similar relative-risk reductions in patients with relatively severe disease as in those with only moderately low bone density. The ability to generalize results based on this principle is essential to the restriction of placebo-controlled trials to participants whose individual fracture risk is reasonably low.
5. The current preclinical testing requirements are generally sound and should be maintained. The tests that have been most informative about adverse effects of drugs have been histological examination, histomorphometry, and mechanical testing. It would be of interest to see whether newer imaging techniques will provide structural information that is correlated with fracture resistance in experimental animals and in humans, and whether information from those techniques will prove to be highly correlated between such animals and humans.
6. Biochemical markers of bone remodeling may be useful in characterizing biological effects and useful in dose selection but they are not mechanical properties of bone, and are not suitable as major endpoints for pivotal trials.
7. The current requirement for one-year phase IIB trials with bone density endpoints has served very well, and should be maintained with exceptions only if the proposed mechanism of drug action makes such a trial meaningless. There are a number of examples of drugs that would have been better developed had the sponsor selected the regimen for phase III based on the one-year bone density endpoint.
8. Further comments on trial design:
  - a. *Non-inferiority trials suffer from all the limitations that have been described in other indications, as well as prohibitively large sample size requirements.*
  - b. *Add-on trials in which patients are allowed to continue prior treatment for osteoporosis may be considered, depending on the characteristics of the test drug and the prior / continuing therapy. One advantage is the information to be obtained about drug interactions. When such a trial design is employed, a sufficient number of subjects who are not treated with other anti-osteoporotic drugs besides the test agent should be included. In other words, this is not a total substitute for placebo-controlled studies. In most cases, add-on trials will not be the primary or pivotal phase III trials, in part because drug mechanisms of action may not be complementary.*

I hope these comments are useful. I will be happy to assist the Division in any way I can in the review of the osteoporosis guidance.