



April 12, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

RE: Docket No. 2004D-0035: Draft Guidance for Industry on the Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis

Merck has participated with health authorities from around the globe in the development of guidance to establish and update clinical and regulatory standards for drug development. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. In addition, Merck has extensive experience in osteoporosis research and treatment. For these reasons, we are pleased to offer comments on the 1994 draft guidance for industry entitled, "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis."

In general, we believe that the draft document has proven to provide useful guidance for the development of products for the prevention and treatment of osteoporosis since it was issued in April 1994. We commend the Agency for its effort to reevaluate its guidance at this time, however, to allow consideration of changes to reflect information that has become available over the last decade.

In the notice and request for comments (69 FR 6673), FDA sought specific comment on two questions. The questions and our responses are provided below:

1. FDA Question 1: Is it appropriate to continue to use placebo controls in fracture endpoint trials?

The placebo-controlled approach avoids the difficulties associated with conducting active-comparator trials, including establishing assay sensitivity, ensuring rigorous trial conduct, and gaining a clear signal for safety evaluation. MRL believes that a benefit/risk (or “clinical equipoise”) analysis provides useful guidance with respect to circumstances in which placebo controls may be appropriate. When one compares the empirically demonstrated treatment benefits of approved therapeutic agents with their known risks across given populations, it becomes clear that placebo controlled trials, while not appropriate in high-risk patients with a prior vertebral or hip fracture, are still reasonable to conduct in moderate risk patient populations corresponding to patients with osteoporosis but without a baseline vertebral fracture (Table 1). Placebo controlled trials in this moderate risk population are justifiable because the absolute risk reduction of a vertebral fracture with the available treatments (RRR = 50%) in this group is low (1-2% annually) (Table 2), and the risk of treatment-related adverse events is of the same order of magnitude. In this population, the annual incidence rate of a hip fracture is typically only 0.5% (Table 1).

An additional ethical principle that appears to be generally accepted is that it is important to minimize the cumulative risk of an individual participant. This may be accomplished in a study that has more patients but is shorter in length. The absolute risk to a patient receiving placebo over the total period of study is lower in the shorter study. For the same reason, it may be acceptable to enroll higher risk patients in a very short placebo-controlled study (e.g., 1 year).

Table 1 - Annual Incidence of Fractures in Placebo Patients

Categories of Risk	Vert Fx	Clin Non-vert Fx	Hip Fx
<i>Higher Risk Patients (+VFx)</i>			
BMD T-score < -4.0 (HIP)	–	–	1.9%
≥ 2 VFx (VERT-MN)	9.7%	5.3%	0.9%
BMD T-score < -1.6 (FIT-1)	5%	5.5%	0.73%
<i>Intermediate Risk Patients (-VFx)</i>			
BMD T-score < -4.0 (HIP)	–	–	0.53%
BMD T-score < -2.5 (FIT-2)	1.4%	4.3%	0.53%
BMD T-score < -2.0 (FIT-2)	1.1%	3.7%	0.35%
<i>Lower Risk Patients (-VFx, T> -2.5)</i>			
-2.5 < BMD T-score < -2.0 (FIT-2)	0.9%	2.7%	0.14%
-2.5 < BMD T-score < -1.6 (FIT-2)	0.6%	2.4%	0.11%
-2.0 < BMD T-score < -1.6 (FIT-2)	0.4%	2.1%	0.07%

Table 2 – Relative (RRR) and Absolute (ARR) risk reduction in vertebral fracture (VF) incidence over 3 years (% of patients) in pivotal trials performed with alendronate, risedronate, raloxifene and PTH, given at the approved dose (alendronate was given at a dose of 5 mg during the first 2 years of FIT) in the treatment of postmenopausal osteoporosis. Three-year incidence was extrapolated from 21 month exposure in the rhPTH (1-34) trial and interpolated from 4.2 years in FIT-2. Extrapolated 3-yr data obtained from Delmas P. et al Osteop Int, 13: 1-5, 2002.

Risk Profile	Agent	Trial	Placebo	Active Agent	RRR	ARR
<i>High</i> (Prevalent VF)	Alendronate	FIT-1	15%	8%	47%	7%
	Raloxifene	MORE-2	21.2%	14.7%	30%	6.5%
	Risedronate	VERT-US	18.5%	13.9%	33%	4.6%
	Risedronate	VERT-MN	34%	21.8%	46%	12.2%
	rhPTH(1-34)	Neer	24%	8.6%	65%	15.4%
<i>Low</i> (Without Prevalent VF)	Alendronate	FIT-2	2.7%	1.5%	44%	1.2%
		T-score <-2.5	4.2%	2.1%	50%	2.1%
	Raloxifene	MORE-1	4.5%	2.3%	50%	2.2%

2. FDA Question 2: Do fracture end-point trials need to be 3 years in duration, or could shorter studies provide adequate evidence of a new osteoporosis drug’s effectiveness?

MRL Position and Justification

Merck believes that in some situations it may be possible to adequately assess anti-fracture efficacy in a time frame of less than 3 years. Whether a shorter time frame is appropriate depends on a number of variables including preclinical safety, preclinical bone quality profiles, the mechanism of action (antiresorption, enhanced formation, or both), the site of fracture (vertebral vs. non-vertebral), the type of fracture (clinical vs. morphometric), endpoints monitored (BMD, BCM, or both), and the periodicity of the dosing regimen (shorter or longer than the typical bone remodeling unit cycle: 1 – 2 weeks of resorption followed by about 2 months of formation). Thus, provided that normal bone quality is demonstrated in preclinical models, the mechanism of action is well-understood, the dosing periodicity is comparable to the physiological anti-resorptive cycle, and other variables are carefully assessed, fracture endpoint trials of less than 3 years duration deserve consideration. Novel clinical trial models in which the rate of fracture in each year of study may be individually assessed, should be considered. In other situations, for example, a new chemical entity with unresolved preclinical safety or bone quality issues, a full 3-year fracture data set or more may be necessary for the full definition of the benefit/risk profile.

Agents with proposed dosing intervals in excess of the duration of their effects on the bone remodeling cycle should be carefully studied to determine whether antifracture effects are continuous between doses and as robust as daily dosing. Some products in development may require higher cumulative doses than would be given on a daily basis.

One needs to carefully assess the risks (e.g. long-term bone safety of higher cumulative doses, and other toxicity related to the greater acute exposure with higher individual doses) versus the benefits (e.g. convenience).

Additional Merck Comment(s):

In addition, Merck would like to suggest the consideration of the following modification of the preclinical aspects of the 1994 Guidance:

Preclinical Issues for Consideration

Preclinical Models

Experimental models of estrogen deficiency osteopenia are now regarded as among the most accurate models of adult human disease. Data now indicate that vertebral body cancellous bone of the 8-10 month old female rat has the same type of remodeling as found in human cancellous bone. Furthermore, the periosteal and endocortical surfaces of cortical bone of adult rats appear to behave similarly to those same surfaces in adult humans. Nonetheless, the adult rat continues to be inappropriate for use in studying Haversian remodeling of cortical bone.

In addition, the adult rabbit may deserve consideration as an animal model that not only possesses both cancellous and Haversian (cortical bone) remodeling, but also, like the sheep, displays estrogen deficiency bone loss on a seasonal basis. Current data suggest that no porcine or canine model is appropriate for the study of estrogen deficiency osteopenia. Though recent data show that some strains of adult mice develop estrogen deficiency bone loss after ovariectomy, no transgenic or knockout mice have been generated that mimic typical adult human osteoporosis.

We also suggest that the Agency consider removing DPA (dual photon absorptiometry) and ashing as recommended techniques in preclinical bone studies, as these techniques have been superseded.

Preclinical Bone Quality

Clinically, bone quality describes the ability of a bone to resist fracture. Bone quality in preclinical studies is thus assessed by coordinated measurements of bone mass and bone strength. "Normal" bone quality is said to occur in pre-clinical studies when the usual relationship of bone strength to bone mass persists during treatment. It is inappropriate to suggest that bone quality is related to microarchitecture, because no firm evidence exists to link microarchitecture independently to osteoporotic fracture in humans. It is further acknowledged that there is a positive relationship of trabecular bone volume to common microarchitectural endpoints.

We also suggest the omission of the terms "Type I" and "Type II" Osteoporosis, as they are no longer used in the field.

Clinical Issues for Consideration

Pretreatment Biopsy

We recommend elimination of the requirement to perform pre-treatment bone biopsies in populations with qualitatively normal bone histology prior to treatment.

Measurement methods in humans

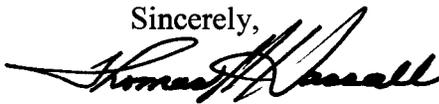
We recommend elimination of recommendations for radiogrammetry, neutron activation, SPA, SXA, and ultrasound. In addition, the value of bone biomarkers as linked to osteoporotic fracture in epidemiologic studies should be upgraded. They are now an integral tool for use in trials of anti-osteoporosis agents.

Treatment vs. Prevention in humans

Merck notes that there is currently some confusion regarding both the requirements for and the timing of an osteoporosis prevention claim in a drug development program. While the current guidance explicitly allows NCE's with estrogen-like qualities to be approved for a prevention claim in the absence of fracture data, we believe this exception deserves reconsideration. Moreover, there may be other products that would effectively prevent bone loss, but not be sufficiently potent to restore lost bone and reduce fracture risk in a patient with severe osteoporosis. It would be desirable for the Agency to open a dialogue to discuss its current thinking regarding the duration of fracture data necessary for approval of a prevention claim as well as the circumstances that may influence whether approval of a product for prevention can precede approval for treatment.

We welcome the opportunity to comment on this draft guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,



for Donald Black, M.D., MBA
Vice President
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