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April 9, 2004

Dockets Management Branch (HFA - 305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket Number 2004D-0035  
Draft Guidance for Industry on the Preclinical and Clinical Evaluation of Agents  
Used in the Prevention or Treatment of Postmenopausal Osteoporosis.**

Eli Lilly and Company (Lilly), as a global research based pharmaceutical company, is committed to the development of innovative medications for the prevention and treatment of osteoporosis.

Osteoporosis is a major public health threat for an estimated 44 million Americans, or 55 percent of the people 50 years of age and older. In the U.S. today, 10 million individuals are estimated to already have the disease, and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis (NOF, 2004).

Lilly applauds the FDA's initiative to update the draft guidance and appreciates the opportunity to comment. Lilly has carefully examined this guidance in general, and with reference to the specific questions related to the duration of fracture end-point trials and the appropriateness of placebo controls. We will address these two specific issues first followed by our recommendations for updating the guidance in general.

**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 and safety?**

There is a need for a common standard for demonstration of efficacy that can be applied to drugs of different classes. Because suitable surrogates for fracture risk reduction have not been validated, Lilly supports demonstration of vertebral fracture risk reduction as necessary to prove efficacy for osteoporosis agents.

However, guidelines should now provide for the acceptability of shorter duration clinical trials (1 to 2 year trials with a vertebral fracture endpoint) for an antiresorptive agent with an established mechanism of action as well as for anabolic agents, provided preclinical studies clearly show no detrimental effect on bone quality. The overall benefit/risk for the investigational agent could be refined based on additional safety information obtained within the clinical program and from post-marketing surveillance programs. The concept of shorter duration fracture studies is supported by published results for several antiresorptives where significant fracture risk reduction has been shown after 1 year in studies that were of 3 to 4 years in duration. While shorter trials may require a

larger sample size to have adequate power, the risk to the individual patient is lessened. Furthermore, in a shorter trial less attrition can be expected improving the ability to assess the investigational agent.

While further guidance is needed on the number of years of follow-up required to assess clinical safety and durability of effect, we believe that a total exposure of 3 to 4 years should be considered appropriate for safety evaluation for agents that are used chronically. Given the chronic nature of the disease and the possibility of long-term treatment, consideration should be given to a requirement for bone biopsies after long-term treatment (for e.g. 3 to 4 years). If biopsies are obtained, histomorphometric parameters should be assessed as well as measurements of bone quality as the state of the art permits.

### **Is it appropriate to continue to use placebo controls in fracture end-point trials?**

While a number of osteoporosis therapies are now available, Lilly maintains that a randomized, placebo-controlled trial with fracture endpoints (using calcium plus vitamin D therapy for all patients) should remain the standard for establishing efficacy and safety. In light of the principles of ethical conduct embodied in the Declaration of Helsinki, a dilemma exists regarding the acceptability of placebo-controlled studies for evaluation of compounds for treatment of a disease for which alternate treatments exist (Brody, 2003, Rosenblatt, 2003). However, a placebo-controlled study that demonstrates superiority of a new drug over placebo may be more useful and ultimately more appropriate than an active comparator design that requires very large study populations and subjects more patients to risk based on uncertainty about the safety and efficacy of the investigational agent. A goal within any study is to minimize risk to individual patients. Given the current state of the field, it is unlikely that patients with multiple fractures or perhaps even one fracture could be included in long-term placebo-controlled trials given the increased risk for re-fracture in these patients. An advantage of a 1- to 2-year placebo-controlled fracture outcome study is that the risk to individual patients would be relatively less compared with participation in a 3-year study.

We also refer to the recent guidance on osteoporosis drug development issued by the European CPMP in 2001. The guidance indicates that although active-control trials are preferred, placebo-controlled trials are still acceptable. Placebo-controlled studies provide greater flexibility in study designs (e.g., use of escape clauses and stopping rules to maximize patient safety, use of add-on therapies) and should be considered for new drugs in development.

There are considerable challenges in conducting active comparator trials rather than placebo-controlled studies. For example:

- Lack of access to data for the active comparator, other than that present in the public domain, may hamper estimation of statistical power and sample size estimations for hypothesis testing.
- Appropriately designed non-inferiority trials would require exposing large numbers of patients in potentially longer clinical trials.
- Trials designed to establish either non-inferiority or superiority of drug compared to an established therapy might be compromised due to difficulty in replicating the

effectiveness of the comparator therapy depending on the population studied and conditions of the trial design. Without a placebo control group, one could not know whether or not the active comparator had worked!

- If an active comparator was required, how would a sponsor determine which therapy is best for comparison, given that different classes of osteoporosis therapies work via different mechanisms, have different pharmacokinetic profiles, and even have different target populations?
- Finally, there may be a lack of understanding of the safety profile because the 'true' adverse event rate for a new drug is best derived from placebo-controlled studies.

Lilly also appreciates the opportunity to comment on other sections of the draft guidance as follows:

### **Clinical Trial Design**

The Agency should take into consideration the diversity of agents currently approved and under development, e.g., antiresorptives (bisphosphonates, SERMs, estrogens etc.) and anabolic agents (i.e., PTH) [Section C. Phase III Studies] when providing clinical trial design guidance. We believe that new estrogens should have the same requirements for approval as any antiresorptive agent. When possible, the clinical plan should address specific features of an investigational agent based on its mechanism of action. Lilly also recommends that appropriately designed Phase 2 trials of 3-6 months duration with bone markers as primary endpoint should be sufficient prior to conducting Phase 3 trials.

### **Hip Fractures and Non-Vertebral Fractures**

It is becoming increasingly evident that it is not practical to perform studies specifically focused to assess reduction of hip fractures. While demonstration of reduction of fractures at the hip is not required by current guidelines in the US, guidance for requirements to include label language, which describe efficacy trends or surrogate efficacy measures at the hip is needed. It is not practical to limit studies specifically to hip fractures. For example, to demonstrate a 40% reduction in incidence of hip fracture assuming a 3% event rate, the number of patients required for a placebo-controlled study is 5000, and for an active controlled non-inferiority study with a 20% margin of non-inferiority, the number of patients required is 33,000. For an active-controlled superiority study, the number of patients required would be 40,000. Therefore, Lilly supports the current approach in labeling that permits display of non-vertebral fracture results by skeletal site. Additional features of a clinical plan that include assessment of skeletal architecture as well as muscle strength and fall risk could become part of the labeling to enhance determination of the benefit/risk of an agent.

### **Sequential and Concomitant Osteoporosis Therapies**

Osteoporosis is a chronic progressive disease and the goal of treatment should be to quickly reduce fracture risk and maintain treatment benefits for as long as possible. With the availability of a variety of therapeutic options, drugs are likely to be used for the treatment of osteoporosis in a number of ways: alone, sequentially or in combinations. Lilly recommends that guidance be provided regarding study designs to provide data for sequential or combined use of osteoporosis agents with the same or different mechanisms of action. We believe that areal and volumetric bone mineral density (BMD) are reasonable and adequate endpoints to demonstrate efficacy for the combination regimen and for assessing maintenance of efficacy when supported by non-

clinical evidence of enhanced bone strength and/or architecture resulting from the combination.

### **Study Population**

Clinical characteristics that contribute to fracture risk independent of BMD include age, previous fragility fractures, elevated bone turnover, premature menopause, history of family hip fractures, and use of oral corticosteroids (Kanis, 2002). Thus, the guidance should be forward looking and should consider basing study entry criteria on 5-10 year probability of fracture risk in lieu of, or in addition to, factors such as BMD thresholds as the state of the art permits. This should include women and men with low bone mass but with bone density higher than a T score of -2 who are also at increased risk of sustaining a fracture (Siris, 2001).

### **Clinical Investigation in Men**

Of the 10 million Americans estimated to have osteoporosis, eight million are women and 2 million are men (NOF, 2004). Guidance is needed on the clinical investigation and registration of products for the treatment of osteoporosis or to increase bone mass in men having osteoporosis of various etiologies. Since gender has not been shown to be an important covariate in response to treatment with non-estrogen receptor acting agents, bridging from fracture data in women may be appropriate.

### **Glucocorticoid-Induced Osteoporosis**

Glucocorticoid use is the most common cause of secondary osteoporosis (Lukert, 1990). Glucocorticoid-induced skeletal deficits reflect a disruption of the normal relationship between the resorption and formation phases of bone remodeling. The consequence of steroid-induced bone loss is bone fragility and an increased risk for low-trauma fractures.

Therefore, a need exists for therapies that can substantially improve bone status of patients with glucocorticoid-induced bone loss. Once a drug is approved for treatment of osteoporosis, Lilly recommends an appropriate study in the target population (men and women) with doses having shown an effect in reducing fracture risk. Treatment-induced change in BMD should be an acceptable endpoint for agents whose fracture efficacy has previously been established.

### **Assessments of Bone Quality**

The current guidance does not consider histomorphometric parameters of clinical bone biopsies as efficacy endpoints. Given the inherent importance of bone architecture to its mechanical properties the Agency should consider providing guidance on use of advanced imaging and computer-based analytical techniques for demonstrating changes in bone microarchitecture (which may be most important during treatment with skeletal anabolic agents) as efficacy assessments. Sponsors should be encouraged to consider new assessments for bone strength that could include measurements of bone tissue intrinsic quality and architecture during clinical development.

Lilly recommends that the revised guidance on osteoporosis emphasize the need to assess bone quality (architecture and mass) to enable advancement in this field. A clear stepwise process should be developed, perhaps with further external guidance, for the identification and validation of architectural parameters that reflect favorable treatment effects.

### **Biomarkers**

The guidance should be updated to reflect advancement in the area of biomarkers and should highlight serum-based markers of bone formation and resorption such as procollagen 1 N-terminal propeptide (P1NP) and C-terminal cross linking telopeptide of type 1 collagen (CTX). Reductions in bone turnover have been associated with reduction in vertebral risk for several compounds; therefore, the utility of bone marker assessment to predict response needs to be further explored (Eastell, 2003, Riggs, 2002, Bjarnason, 2001). The utility of different CTX fragments in predicting future osteoporotic fractures has been evaluated and can be further explored in clinical trials (Garnero, 2002).

The guidance should also harmonize with the Agency's view on genomics and proteomics to enhance safety and perhaps to identify patients most likely to have a favorable benefit/risk during treatment.

### **New Route of Administration and New Formulations**

Guidance is needed on the clinical study design, duration and endpoints for new formulations and new routes of administration. Treatment-induced change in BMD should be an acceptable endpoint for new formulations for compounds whose fracture efficacy has previously been established. Lilly recommends that non-inferiority with respect to BMD should be demonstrated for the new dose or formulation compared to the dose effective in reducing fractures. Lilly recommends a shorter duration clinical trial (1 year) with appropriate follow-up safety assessments depending on the route of administration.

### **Use of lateral vertebral assessment (LVA) and instant vertebral assessment (IVA) Images**

In recent years there has been increased interest and investigation into the clinical use of dual-energy x-ray absorptiometry (DXA) images for the detection of vertebral fractures. The use of LVA/IVA technique to detect vertebral fractures in clinical trial subjects is attractive because it would result in lower radiation exposure compared with routine spinal radiographs and could reduce the number of study procedures for patients (Ferrar, 2003). Further use of the technique in a clinical trial would also allow ascertainment of the time-dependence of vertebral fracture risk reduction during treatment that could be correlated with height loss and back pain. The guidance should include a clear and efficient path for validation of new surrogates that can simplify clinical development.

### **Harmonization of Guidelines**

There will be a critical need for harmonization of guidelines between the various regulatory agencies to provide for similar registration requirements across countries and regions. Divergent guidelines will make registration of new osteoporosis therapies needlessly expensive and difficult. Therefore, it will be important to keep communications open with the CPMP, the MHLW, and with public health agencies such as the NIH to address these critical questions and provide recommendations for workable new guidelines for developing osteoporosis therapies.

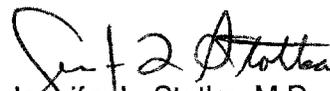
Again, we appreciate the opportunity to comment on the revision of the 1994 draft Guidance. Eli Lilly and Company looks forward to working with the FDA to ensure the availability of safe and more effective products for the prevention and treatment of osteoporosis, a common and devastating chronic disorder of our aging population.

Sincerely,

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