GUIDELINES FOR PRECLINICAL AND CLINICAL EVALUATION OF AGENTS USED IN THE PREVENTION OR TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

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Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706
(301)827-6430

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Table of Contents

	Page
Preclinical Evaluation	
I. Introduction	2
II. Study Design	3
III. Animal Models	3
IV. Biochemical Markers of Bone Turnover	4
V. Bone Mass/Density Measurement	4
VI. Analysis of Bone Architecture/Histology	5
VII. Biomechanical Testing of Bone Strength	5
VIII. Regulatory Aspects	5
Clinical Evaluation	
I. Introduction	6
II. Clinical Studies	8
III. Study Duration and Assessment of Efficacy	11
IV. Procedure and Evaluation	16
V. Statistical Consideration	18
VI. Safety Testing	20
VII. Guide to FDA Action on NDA for Osteoporosis	21
VIII. Issues Related to Testing of Combined Drug Regimens	22
IX. Research Priorities in Postmenopausal Osteoporosis	22
X. References	23

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Preclinical Evaluation

I. Introduction

In addition to the toxicity studies required for all new drugs (see CFR 312.23(8)), preclinical studies of bone quality should be performed for drugs to be used in the prevention and intervention of osteoporosis. For these guidelines, bone quality is considered to be comprised of the architecture, mass and strength of bone. These studies are warranted by instances in which bone density was not positively correlated with architecture and strength. Non-invasive techniques for assessing bone strength clinically (such as ultrasound) have not been adequately validated, but animal studies provide an opportunity to directly examine bone mass, architecture and strength. Thus, the primary objective of these studies is to demonstrate that long term treatment with a specific agent will not lead to deleterious effects on bone quality.

The proposed animal studies will permit early identification of drugs that result in abnormal architecture or in production of bone in which strength is not positively correlated with density and architecture. It may be possible to identify doses that control excessive bone resorption without suppressing osteoblast activity. These preclinical studies of bone quality might demonstrate efficacy in animals, but clinical efficacy must still be established.

Because no single animal species duplicates all the characteristics of human osteoporosis, it is felt that an examination of bone quality in two species is necessary to adequately investigate the effectiveness and safety of drugs for this indication. One study should be conducted in the ovariectomized rat model and the second in a non-rodent model (i.e., larger, remodeling species) which will be left to the discretion of the sponsor although there is evidence that the dog may not be a good model[1]. Parameters to be monitored in these studies include biochemical markers of bone resorption and formation, histomorphometric analysis of bone architecture, measurement of bone density and biomechanical testing of bone strength. Histomorphometric, densitometric and biomechanical analyses should be performed on both long bones (femur and tibia) and lumbar vertebral bodies. Whenever possible, the parameters and techniques that will be used to demonstrate clinical efficacy should also be pursued in the preclinical studies. Further recommendations on these studies are detailed in the subsequent sections.

II. Study Design

Time of initiation of treatment in preclinical studies should be reflective of the clinical indication. Specifically, time of initiation of treatment will be different for studies designed for the prevention of osteoporosis versus intervention for the treatment of osteoporosis. In a prevention study using an ovariectomized animal model, treatment should be initiated immediately after ovariectomy. In an intervention type study, significant cancellous bone loss following ovariectomy should be demonstrated prior to initiation of treatment. The animal studies should be of the same type as the indication being sought. For example, an intervention indication should be supported with intervention studies in animals. Likewise, for a prevention indication, there should be animal studies for the prevention of osteoporosis. However, successfully completed preclinical studies for one of these indications will usually be sufficient to support clinical studies of the other indication.

Treatment schedule (continuous vs. intermittent) to be used in the preclinical studies should be the same as that intended for clinical use. If the drug is to be used intermittently, then the preclinical studies should be adjusted to reflect the same relative treatment duration during the bone resorption/formation cycle as that proposed clinically. The animals should be treated with two doses; one that is optimally effective in that species, and one that is approximately 5 times greater. The optimally effective dose should be determined in a dose range-finding study using biochemical parameters or bone mineral density (BMD) as endpoints. Studies using a dose that is optimally effective in the animal should provide the most relevant information on the correlation between BMD and bone strength for that particular drug and a dose 5 times greater should give an indication of the margin of safety.

The duration of preclinical studies should be based primarily on bone turnover (number of complete resorption and formation cycles/year) of a species and should consist of a number of cycles equivalent to 4 years of human exposure. For example if bone turnover in humans is 100-200 days or 2-4 cycles/year[2], and in rats[3], baboons[4] and cynomolgus monkeys[5] is approximately 40 days or 9 cycles/year, then 16-month studies in rats and primates are comparable to 4 years in humans. Because of the relatively short life-span of rats, the treatment duration for this species may be limited to 12 months.

III. Animal Models

Animal models for osteoporosis may be classified as either modeling (rats) or remodeling (examples include dogs, ewes, and primates). Modeling of bone is the method by which bone grows and is shaped. In remodeling species, including adult humans, bone undergoes a continuous coordinated process of bone

resorption, followed by formation of new bone. The modeling and remodeling species have been further classified as models of accelerated bone loss and of decreased bone formation. Examples of models of accelerated bone loss include castrate male rats and acute post-ovariectomized female rats (modeling species), lactating pigs and ovariectomized primates (remodeling species). Models of decreased bone formation include aged rats or mice and glucocorticoid-treated rats (modeling species), and aged canines or primates and glucocorticoid-treated pigs (remodeling species). Additionally, the literature contains reports of transgenic mice and congenitally osteoporotic mice as potential new models of osteoporosis.

At the present time, an experimental model that precisely mimics the pathophysiology of postmenopausal osteoporosis is unavailable. Although several risk factors for osteoporosis have been identified, there is a predominant association with estrogen-deficiency. Hence, ovariectomized animals are the preferred animal models to provide insight into the clinical outcome of an anti-osteoporotic drug.

As stated previously, preclinical studies of bone quality in two species are required. One of these studies must be performed in the ovariectomized rat model (modeling species). Although differences in bone metabolism exist between rats and humans, the rat model has been reported to be an appropriate model for cancellous bone changes in humans. The second study should be performed in a larger, remodeling species. The animal model used in the second study is at the discretion of the sponsor. However, the rationale for choosing the specific model should be clearly stated.

IV. Biochemical Markers of Bone Turnover

A general discussion of biochemical markers of bone turnover can be found under section II of the clinical guidelines. In preclinical studies, at least one biochemical marker each for bone resorption and formation should be measured. A suggested biochemical marker of bone resorption is urinary pyridinium cross-links and of bone formation is serum heat-labile alkaline phosphatase (bone-specific isozyme). Measurement of serum osteocalcin (specific marker of bone formation) is also encouraged.

V. Bone Mass/Density Measurement

Any of the techniques listed below may be used to monitor skeletal mass/density changes in the preclinical studies. Bone mass in small animals has commonly been determined by bone ash weight. Non-invasive clinical techniques for measuring bone mass such as DPA, DEXA and QCT, have also been applied in rats. In rat studies, substantiation of bone mass data from non-invasive methods with bone ash weight is recommended. Descriptions of the

absorptiometry and tomography techniques can be found in section II, item 1 of the clinical guidelines.

1. Bone ash weight
2. Single photon absorptiometry (SPA)
3. Dual photon absorptiometry (DPA)
4. Dual energy x-ray absorptiometry (DEXA)
5. Quantitative computed tomography (QCT)

VI. Analysis of Bone Architecture/Histology

Suggested techniques for the animals studies are listed below. Relatively simple microscopic techniques include tartrate-resistant acid phosphatase staining of osteoclasts and the use of polarized light to examine collagen fiber arrangement in bone. More sophisticated histomorphometric analysis utilizes tetracycline labeling of bone to obtain information on the dynamics of bone remodeling such as activation frequency, bone formation rate and mineral apposition rate.

1. Light microscopy

2. Polarized light microscopy

3. Tetracycline-labeling of bone

VII. Biomechanical Testing of Bone Strength

The three main types of biomechanical tests for bone strength are bending, torsional and compression tests. Bending (3 or 4-point) and torsional testing are usually performed on long bones and compression tests are applied to vertebral bodies. Both long bones and vertebral bodies should be tested, since it is unclear whether data on strength of long bones will be reflective of that in vertebrae. For a detailed discussion of biomechanical testing of bone, see Turner & Burr, 1993.[6] Details of the testing procedure and definitions of terminology used should be included in the study protocol.

VIII. Regulatory Aspects

Protocols for the bone quality studies should be submitted well in advance of the study initiation date. Discussions of specific details of study design are encouraged. In general, final reports of the preclinical bone quality studies should be submitted by the end of Phase III prior to the NDA. The following flow chart indicates the scheduling of preclinical bone quality studies, relative to the clinical development of a drug:

Pre-IND Meeting
(Discussion of Preclinical and Clinical Requirements)

Phase I
(Single and Multiple Dose Safety/Tolerability
and Pharmacokinetic Studies)

Submission of Protocols for Preclinical Studies of Bone Quality

Phase II
(Dose Ranging Studies)

End of Phase II Meeting

Phase III
(Demonstration of Clinical Efficacy and Safety)

Pre-NDA Meeting

Submission of Final Reports from Studies in Rats and non-Rodents

Submission of NDA

Clinical Evaluation

"General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed prior to reading these guidelines. It contains suggestions that are applicable to the evaluation of most classes of drugs in all age groups. In addition, the "Guideline for the Study of Drugs Likely to be Used in the Elderly" and the "Guideline for the Format and Content of the Clinical and Statistical Section of an Application" are also recommended for review prior to reading of these guidelines.

I. Introduction

For the purpose of these guidelines, osteoporosis is defined as a condition in which the bone mass per unit volume (density) of normally mineralized bone is reduced. However, reduced bone mineral density is not the only abnormality associated with reduced bone strength. The bone may no longer provide adequate mechanical support and there is a high risk of fracture without trauma or in response to minimal trauma.

Although osteoporosis may be associated with and secondary to a variety of systemic disorders such as Cushing's syndrome, hyperthyroidism, or immobilization, an associated disorder of etiological significance cannot be identified in most patients. There is an age related net loss of bone that usually begins during the fifth decade in most, if not all, people. Attempts

have been made to divide involutional osteoporosis into two separate syndromes (Type I and Type II). This concept of two syndromes, though not universally accepted, may serve as a useful tool in selecting a treatment regimen. Type I osteoporosis affects women after menopause and results from an accelerated rate of bone loss (mainly trabecular) due to factors (mostly estrogen deficiency) related to menopause. Vertebral "crush" and distal radius fractures are common in Type I osteoporosis. Type II (age-related) osteoporosis involves both men and women over age 70 and is characterized by gradual (over several decades) loss of both trabecular and cortical bone mass due to factors related to aging process. In women with Type II osteoporosis, estrogen-deficiency also contributes to the overall bone loss. Both vertebral (multiple wedge type) and hip fractures are common in Type II osteoporosis.

Loss of bone mass in osteoporotic patients (Type I) generally involves the entire skeleton including cortical and trabecular portions of both axial and appendicular bones. Rate of bone loss may vary, and bone loss may be more advanced in some skeletal locations than in others. During the first five to ten years after menopause, bone loss occurs at an accelerated rate. Thereafter, bone loss continue at a slower rate for up to 20 years.

Many patients with osteoporosis are asymptomatic. Episodic back pain may be coincident with vertebral fracture, but such fractures frequently are not associated with pain. Chronic pain generally is attributed to muscle spasm, nerve root irritation, and/or degenerative arthritis secondary to previous fracture and bone deformity. A significant vertebral deformation is generally needed to cause marked back pain and immobilization.

The most important morbid event in osteoporosis is fracture. The common fracture sites include proximal femur (hip), vertebrae, distal radius, proximal humerus shaft, and ankle. In epidemiologic studies, bone mineral density (BMD) has predicted the risk of vertebral fracture. However, a treatment related increase in BMD cannot be assumed to result in reduced risk of fracture. For example, the relationship between BMD and fracture risk has been validated only for patients receiving estrogens, and does not apply to patients receiving fluoride.

Assessment of the effect of a new drug regimen on the incidence of new vertebral fractures is of primary importance in judging efficacy. Various definitions of incident vertebral fracture have been proposed. Specific and objective criteria for determining the baseline number of prevalent vertebral fractures must be detailed in study protocols.

Drugs covered in this outline are those that are intended to affect the rate of fracture occurrence or the underlying rate of bone loss or accretion in osteoporosis, and not those that are

expected to affect symptoms directly, e.g., analgesics. Drugs intended for prevention and/or treatment of osteoporosis may be classified either by their chemical characteristics (e.g., vitamin D metabolites/analogues, peptides and estrogens) or by the mechanism of action.

II. Clinical Studies

A. Phase I Studies

Pharmacokinetic and pharmacodynamic studies should be conducted as discussed in "General Considerations for the Clinical Evaluation of Drugs."

B. Phase II Studies

Phase II studies should include twelve month, double blind, placebo-controlled, parallel group studies to establish the minimal effective dose and dose-response curve. For improvement or stabilization of vertebral BMD a target difference from placebo in change from baseline in BMD should be specified in the protocol. Biochemical markers of bone turnover should be measured along with vertebral BMD in dose-ranging studies, since such measurements may help in determining dosage of the test drug that achieves the optimum response.

Trials to investigate the biologic actions of a drug and the mechanism involved in actions (rather than to demonstrate safety and effectiveness directly) are usually performed in representative individuals who are carefully studied under a separate protocol. Some of the tests listed under safety might also be a part of pharmacodynamic testing, and some tests included here could be broadly interpreted as safety tests.

The following tests are recommended for studying pharmacodynamic actions of a drug:

1. Serum parathyroid hormone (iPTH).
2. Serum vitamin D metabolites, 25-(OH)D and/or $1,25(OH)_2D$.
3. Urinary hydroxyproline and/or other bone matrix components.
4. Calcium balance studies and/or other methods quantitating intestinal calcium absorption.
5. Bone biopsy with quantitative static and dynamic

histomorphometry at baseline and after 3 years treatment and/or at end of the study.

C. Phase III Studies

It is anticipated that studies for treatment of established osteoporosis will be initiated, and that interim data from such studies will be available, along with appropriate data from preclinical studies in two species prior to initiation of trials for prevention of osteoporosis. Specific efficacy and safety requirements for the prevention study should be discussed with the Agency. The recommended primary efficacy endpoint(s) for prevention and treatment studies are as follows:

Investigational Drugs	Prevention	Treatment
Estrogens	Bone Mineral Density	Bone Mineral Density*
Non-Estrogens	Bone Mineral Density§	Fracture Evaluation**

* Epidemiological studies have demonstrated that estrogen therapy reduces the risk of vertebral and non-vertebral (femoral neck and distal radius) fractures. Therefore, fracture evaluation for estrogen preparations is not required for the treatment study.

** See table on page 18.

§ Other supporting efficacy endpoints for Phase III studies should be discussed with the Agency. Ordinarily, bone mineral density, alone, as an endpoint will be sufficient for approval of the prevention indication only if efficacy has already been demonstrated in a treatment study with a fracture endpoint.

1. Drugs for Treatment of Patients with Established Osteoporosis:

a. Study design: Studies of treatment of osteoporosis in patients with fractures should be double-blind and randomized, with either placebo or active drug in the control group. However, the use of an active control drug requires extra precautions in planning the study. Sample size calculation must provide assurance that the study will enroll enough patients to detect a meaningful difference between the test drug and active control if such a difference exists. In addition, unless adequate background information is submitted to document that the active control performs better than placebo in studies with similar size and similar patients using the same endpoint measurement technique, it will be necessary to

show that the test drug performs better than the active control.

b. Study population: Candidates for a postmenopausal osteoporosis treatment study are ambulatory out-patients at least 5 years postmenopausal, with one or more osteoporosis-related vertebral fractures and/or with lumbar vertebral BMD $\geq$ 2 S.D. below the mean peak BMD for premenopausal women. Candidates will usually be at least 60 years of age and have symptoms and signs such as bone pain and loss of height. However, signs and symptoms alone are not considered adequate criteria for inclusion of patients in the study.

Patients who have conditions that play a significant etiologic role in the development of osteoporosis (due to immobilization or glucocorticoid-induced) should be studied separately.

Other exclusion criteria:

i. Diseases which may affect bone metabolism, e.g., hyper-or hypocalcemia, hyperthyroidism, osteogenesis imperfecta, malignancy, chronic gastrointestinal disease, extensive Paget's disease, alcoholism, and renal or hepatic impairment.

ii. Drug therapy for osteoporosis within the previous six months (excluding calcium supplements).

iii. Chronic or continued use of medication that may affect bone calcium metabolism, for example, phosphate-binding antacids, many diuretics, adrenal or anabolic steroids, heparin, anticonvulsants, fluoride in excess of 1 mg/day and supplements of vitamin D or A in excess of RDAs. Estrogens and progestins should not be used unless they are part of the treatment protocol.

iv. Evidence of osteomalacia on diagnostic bone biopsies. Such biopsies are necessary to exclude osteomalacia if the study population is likely to have osteomalacia (e.g., hip fracture or institutionalized patients).

v. Vitamin D deficiency. 25-hydroxyvitamin D should be determined in all patients, and 1,25-dihydroxyvitamin D determination may be of value in some instances.

2. <u>Drugs for Prevention of Bone Loss in Asymptomatic Patients:</u>

a. Study Design: If a drug has been approved for the treatment of osteoporosis, BMD may serve as an appropriate efficacy endpoint in trials for prevention of

osteoporosis . Efficacy trials should be randomized, double-blind, placebo-controlled with multiple dosage arms to enable assessment of the minimum effective dose. The study should last for at least 2 years. The minimum sample size that is calculated to adequately address safety and efficacy should be discussed with the Agency.

b. Study population: Prevention studies should be carried out in groups of postmenopausal (1-3 yrs post cessation of menses) ambulatory out-patients between ages 45 and older who do not yet have osteoporosis, or ovariectomized women who have documented elevated FSH (•50 mu/ml) with low serum estradiol (• 20 pg/ml). Enrollment of patients who are at risk of developing postmenopausal osteoporosis is appropriate.

III. Study Duration and Assessment of Efficacy

Demonstration that an agent reduces vertebral fracture frequency can be obtained from a double-blind, randomized study with concomitant placebo controls. Depending on the anticipated efficacy of the proposed drug and the difference that is expected between the fracture rates in the treated and control groups, the studies may require a relatively large number of patients. The requisite number of subjects in fracture endpoint studies will be influenced by the anticipated rate of new fractures in the control group over the course of the study. Incident fracture risk of study subjects may be assessed in the following strata:

1. Patients with low or intermediate vertebral BMD with 1 or more baseline fractures.

2. Patients with low/very low vertebral BMD without fractures at baseline.

As noted above, demonstration that an agent preserves or enhances bone mass provides only suggestive evidence that it reduces fracture risk; fracture studies must be done to document reduction of fracture incidence. A drug approval may be based on three year clinical data, if 1) preclinical studies clearly show no detrimental effect on bone quality (including bone histology, density and strength), 2) fracture data after 3 years of treatment show at least a trend ($p<0.2$) toward decreased fracture incidence and no deterioration in the third year, 3) a subset of trial subjects that are subjected to bone biopsy (before treatment and after 3 years of treatment) show no abnormality of bone, and 4) bone mineral density is enhanced to a degree that is statistically and clinically significant. If approval is granted on the basis of this three-year clinical data, the fracture study must be continued post-marketing to 5 years or as needed to show fracture reduction. For new formulations of calcium or estrogens, BMD will be an adequate primary efficacy endpoint provided toxicity is acceptable and the lowest dose that is

maximally effective has been determined.

We encourage serial assessment of stature in Phase III trials of anti-osteoporotic drugs using a stadiometer and standard protocol for multiple, repeated measures at periodic visits. Since changes in stature may reflect disease of intervertebral disks rather than decrease in vertebral heights, statural changes should be considered as supportive data rather than a primary efficacy variable.

An agent demonstrated to have favorable direct effects on bone mass in osteoporosis and to reduce fracture frequency would also be expected to reduce the pain and disability associated with the disease. Although pain and disability are of obvious importance, obtaining meaningful data on these parameters during clinical trials is difficult and requires carefully designed, randomized, double-blind studies. Because pain and disability could be influenced by actions not related to a direct effect on bone and the primary osteoporotic process, data demonstrating a favorable effect on these parameters should be considered as supportive of, and not a substitute for, bone mass and fracture frequency data.

A. Evaluating Skeletal Mass

All currently available methods for the noninvasive assessment of bone mass or bone mineral density (BMD) have some disadvantages, and experts may disagree about the relative adequacy of different methods. It is desirable to measure cortical and trabecular bone mass separately in the appendicular and axial skeleton at several different locations, including locations that are prone to osteoporosis-related fractures. Fractures are expected at the sites where these measurements are performed (e.g., the distal radius or the neck of the femur), but other factors (e.g., qualitative defects in bone structure, trauma due to falls) are also responsible for these fractures. Falls play an important role for the distal radius and hip fractures.

The accuracy of the techniques used to measure bone mass must be established by comparing the results of *in situ* measurements with chemical measurements of the same bones, or by making an equivalent comparison. A measurement technique that lacks absolute accuracy, may nonetheless be useful for serial measurements of bone mass if precision is high. Data on test-retest reliability of the bone density measurement technique should be presented and the overall measurement process at each particular study site should be assessed and described. Laboratories should establish with reasonable confidence that serial changes in the measured bone mineral density reflect changes in bone mass rather than changes in bone marrow or extraskeletal tissues. Multiple scans at each time point improve the reliability of determining the rate of change in BMD. The principal techniques currently available for evaluating skeletal mass are the following:

1. Single-energy photon absorptiometry (SPA) measures the absorption of a monochromatic photon beam by bone mineral in vivo, usually of the radius (of non-dominant arm), os calcis, metacarpals, or phalanges. This method estimates cortical and trabecular bone mass combined and is capable of generating highly reproducible data although considerable care must be taken for accurate repositioning on subsequent measurements. Bone mass determined with this method correlates poorly with vertebral trabecular bone density, and only moderately well with femoral neck fracture frequency. Most authors have found accuracy error of this method in the order of 4%-5%. The precision is 1%-3% when the standard cortical site (e.g., one-third of the distance from the ulnar styloid to the olecranon) bone mass is measured. The radiation exposure to the site of measurement is < 15 mrem with a negligible radiation to the whole body.

2. Dual-energy photon absorptiometry (DPA) measures simultaneously the attenuation of photons at each of two energies of a bichromatic photon beam by skeleton and extra skeletal tissues in the torso or extremities. If the energies of the two photons (from ^{153}-gadolinium) on the beam differ appropriately, correction for the attenuation due to soft tissue may be made and attenuation due to skeletal tissues is accurately estimated. An imaging device is necessary to allow accurate repositioning on subsequent measurements. Care should be taken that, where possible, areas of extraskeletal calcification do not overlie bone that is being scanned. Bone mineral density of spine, proximal femur, other long bones, and whole body can be measured by this method. The result is usually expressed as an "areal density of grams of total mass of bone within the area chosen (g/cm^2)". The precision of DPA with a relatively new source of energy is in the order of 2%-4%, and the accuracy is about same as in the case of SPA[6].

3. Dual energy x-ray absorptiometry (DEXA) uses an x-ray source of energy instead of an isotope source used in DPA and it has all the advantages of DPA. The use of an x-ray source results in stable output (no decrease in source strength with time as seen with isotope), better image resolution with a faster scanning speed (shorter scanning time), and smaller radiation exposure.

4. Quantitative computed tomography (QCT) is based on a principle similar to that of absorptiometry, in that it relies on the "greater absorption of ionizing radiation that passes through calcified tissue." It makes precise anatomical localization possible and measures trabecular bone separately from cortical bone. In x-ray computed tomography the measured CT values are compared with those

obtained from reference standards containing known concentrations of K_2HPO_4 or aluminum spine phantom. The results of QCT scan are expressed in mg of mineral equivalent/ml of trabecular bone volume (bone trabeculae plus marrow). In aging vertebral trabecular bone the presence of excess fat in the marrow introduces error to the extent of 7%-15% per 10% fat. This problem can be resolved to a great extent by using a dual energy scanner. However, the radiation exposure is increased two-fold with the use of the latter scanner. Both accuracy error and precision (coefficient of variation) for this technique are in the order of 5%-8%.

5. Radiogrammetry measures bone shaft cortical thickness on standardized radiographs, generally of the metacarpals, radius, humerus or femur. Its advantages include ease of performance, relatively low cost, reproducibility, and its adaptability to large multi-center studies. Only small segments of the skeleton are measured, however, and the technique does not provide information about trabecular bone. This technique may be used in research studies, but not recommended for the efficacy clinical trials.

For all of the above-mentioned techniques, instrument precision is very important. To achieve optimal instrument precision, a. Stability of the instrument should be tested periodically throughout the study, b. Duplicate measurements should be performed at relatively short-time (less than one week) intervals in subjects, in order to minimize errors due to positioning and individual technician's measurement errors, and c. Changes in body composition and configuration (scoliosis, spinal deformities) should be considered. The sites of successive measurements, particularly in relation to proximal hip should be matched.

Currently, DEXA seems to provide the greatest choice in sampling sites, relatively better precision and less radiation burden. For the measurement of bone mineral density in postmenopausal osteoporosis, lumbar spine and proximal femur are the most relevant skeletal sites. Repeated measurements of BMD in a long-term study allow assessment of the rate of bone loss in response to a treatment regimen.

6. In vivo neutron activation analysis estimates bone calcium content by activating trace quantities of ^{48}Ca, a naturally occurring stable isotope in bone mineral. A major limitation of this technique is that few facilities are capable of performing these analyses, and the radiation dose is much greater than that of other radiographic methods. The method is further limited in

that cortical and trabecular bone and extraskeletal calcium cannot be separately quantitated (the entire skeleton consists of 85% cortical and 15% trabecular bone).

In recent years, several other techniques such as ultrasound and nuclear magnetic resonance have been developed to measure the bone mass and quality (elasticity and architecture). Bone turnover has been estimated by kinetic studies with stable or radioactive isomers of calcium as well as with other bone-seeking elements. These techniques have made important contributions to research, but their routine use in clinical trials is not yet clearly delineated.

B. Other Measurements

1. Bone biopsy. Various quantitative procedures have been applied to biopsied bone including measurements of trabecular bone volume and mass. Disadvantages are: 1) the biopsied bone represents only a very small portion of the skeleton, 2) there is considerable variability among different sites in the same individual, 3) it is not possible to sample the identical site twice, and 4) it is a surgical procedure causing some discomfort to the patient. It provides a means of recognizing osteomalacia, and of determining whether the bone formed during treatment is histologically normal. Histomorphometric parameters of bone biopsy are not considered as efficacy endpoints in clinical trials.

2. Calcium balance measurements, although sensitive and simple in concept, are costly, time consuming, and difficult to perform well. Each calcium balance period should be continued for at least 7 days, and several such periods are needed during the course of the study to give useful data to follow response to treatment.

Bone biopsy and calcium balance studies can give valuable supportive information for evaluating agents, but are not acceptable as the sole techniques for evaluating the response of bone mass to treatment and to determine the minimum effective dose of an agent.

3. Biochemical markers of bone turnover are being increasingly used in clinical trials to monitor response to therapy in osteoporosis as well as in other metabolic bone diseases. These markers provide information at the total skeletal level regarding bone formation and resorption. The commonly used biochemical markers are serum heat-labile alkaline phosphatase and urinary hydroxyproline for bone formation and resorption, respectively. However, these markers are not bone specific; therefore do not reflect precisely the changes

in bone remodeling in osteoporotic subjects before and after treatment. Serum osteocalcin (a specific product of osteoblasts also known as bone Gla protein) is a sensitive marker of bone formation. Urinary pyridinolines, hydroxylysyl pyridinoline (or simply pyridinoline) and lysyl pyridinoline (or deoxypyridinoline) are collagen breakdown products (pyridinoline cross-links). They are reported to be more sensitive and responsive markers of bone resorption than hydroxyproline. Measurement of serum osteocalcin and urinary pyridinoline cross-links provides important information regarding bone turnover rate in response to anti-osteoporotic therapy. Biochemical markers of bone turnover may be useful to establish preliminarily the dose that is to be used in BMD or fracture studies.

IV. Procedure and Evaluation

A. Procedure

Dietary instruction should be given to assure that each patient has adequate daily calcium (equivalent to 1500 mg of elemental calcium, either in diet or diet plus calcium supplement) and vitamin D intake. It should be reassessed during treatment to ensure that intake remains constant.

Nutritional status, including body weight should be evaluated to exclude malnourished and morbidly obese subjects. Stratification based on body weight may be necessary in smaller studies.

All patients should receive general instructions regarding daily physical activity (including weight-bearing exercise) with the object of minimizing the risk of osteoporotic fractures.

B. Evaluating skeletal mass (lumbar spine, proximal femur, forearm)

Assessment of bone mass should be performed (on at least two occasions if feasible) before treatment is initiated, and should be repeated at intervals appropriate for the method used during the study.

Each investigative site should run its own long-term quality control and participate in cross-calibration using hydroxyapatite and appropriate "gold-standard" phantoms, respectively.

C. Assessing fractures

Qualitative and objective (morphometric) criteria for defining and detecting prevalent and incident vertebral fractures should be described in detail in the protocol. For trials of the treatment of osteoporosis, assessment of baseline vertebral deformity must be based on established morphometric criteria and/or the presence of one definite fracture determined by qualitative assessment by a radiologist with expertise in the radiological diagnosis of osteoporosis. Incident vertebral fractures should be determined by both morphometric and qualitative radiologic assessments. Greater weight should be given to morphometric measurements.

Incident fractures in previously undeformed vertebrae should be combined with worsening of previously deformed vertebrae in the primary assessment of new fracture rates. Worsening of pre-existing fractures must be defined in terms of a minimal decrement in A/P height ratio or in (+/- T4 normalized) absolute vertebral height measurements, rather than the exceeding of a cutpoint used to establish prevalent fractures. New and worsening fractures should be reported separately.

Morphometric determination of fractures (based on ruler/caliper of digitized measurement of anterior, middle and posterior height for each vertebrae from T4-L5) may be more sensitive than qualitative clinical radiological assessment. A common contributor to measurement error is inconsistency in the numbering of vertebrae. Vertebrae on all baseline and follow-up films for a given patient should be numbered in one sitting by an expert radiologist or other highly qualified and well-trained individual, under the supervision of an expert radiologist. The morphometric vertebral height measurements should be made with the reader blind to the temporal sequence of the films. Both qualitative and morphometric assessment of fractures should ideally be performed in a central reading facility, in a multi-center trial. Also, a second reader may examine all or a representative sample of the film sets to determine the inter-reader consistency in height measurements.

Fractures may be defined either in terms of decrements in anterior, mid, or posterior vertebral body height, and/or by decrement in the ratio of anterior to posterior height (A/P ratio). Absolute measurements may be normalized using T4 (or T5 if T4 is deformed) height in order to correct for magnification differences between films. The threshold of A/P ratio or change in height must be defined in relative and absolute terms (i.e., fracture = •20% decrease in A/P ratio and absolute decrease of •3mm in anterior or mid height).

The proper choice of minimum morphometric change used to

define fracture should result in optimal sensitivity and specificity. Knowledge of the intra-patient variability in the overall measurement process (i.e., from serial spinal radiographs taken in short time intervals) of assessing vertebral height will allow a rational choice for identifying the critical decrement(s) in vertebral height and/or A/P ratio necessary to define "true" fracture. Reproducibility data for morphometric measurements should be obtained for each study site. The minimum threshold of change for defining new fractures may differ for each vertebral level and may differ between study sites.

Non-vertebral fractures should be classified according to type, trauma (if any), location, and severity. Radiographic evidence of previous fractures should be documented carefully at the time patients are entered into the study.

For each patient, the procedures for serial vertebral x-rays and criteria for assessment of deformity/fracture should be identical during the course of the trial.

Interpretation of coded radiographs should be done blindly (regarding treatment assignment and serial order of x-rays).

V. Statistical Considerations

A. Study Design

The clinical efficacy studies should be randomized, double-blind, parallel, placebo or active controlled trials. Crossover and historical control studies are inappropriate.

Randomization procedures should be employed to achieve comparability with regard to prognostic or risk factors which correlate with subsequent subject response or outcome. For example, assignment to randomized treatment groups may incorporate blocking subsequent to stratification according to number of baseline fractures, years elapsed since menopause and levels of baseline bone mineral density.

B. Statistical Power

The sample size should be adequate to detect clinically meaningful (between-treatment) group differences with respect to the primary efficacy parameters.

C. Data Analysis

If an active control group design is employed (with

adequate background documentation of the reproducibility of the efficacy of the active control agent in the study population), the study should be analyzed using a confidence interval difference approach for the between-treatment-group difference. Such an approach will allow evaluation as to whether the upper limit of the confidence interval of the difference in efficacy between active and test regimens exceeds the previously identified clinically significant threshold.

Data should be analyzed and summarized for each major type of fracture (e.g., vertebral, radial, femoral, and rib) in addition to a combined analysis for all types. The combined (fracture analysis) should exclude all, or at least all asymptomatic vertebral fractures. If symptomatic vertebral fractures are included, then a strict protocol definition must be used.

The proportion of patients with at least one fracture should be the primary endpoint. Analysis should also be conducted with regard to the worsening of vertebral fractures. Life table analysis regarding time to first fracture is more appropriate than just comparing fracture incidence rates without taking into consideration the time on treatment. Due to the known relationship between the likelihood of new fractures and the number of existing fractures, statistical analysis which adjusts for the number of existing fractures at baseline should be performed if the average number of fractures per patient is an additional selected endpoint.

Plans for imputing missing data (both fracture follow-up assessment and BMD data) should be explained in the protocol, and one or more supplementary intent-to-treat analyses using imputed data should be performed.

In most cases, serial data on bone mineral density should be used to determine regression parameters for each patient. One should then examine the distribution of these parameters between treatment groups for significant differences.

The association between baseline bone mineral density, change from baseline in bone mineral density and number of baseline fractures, as well as the incidence of new and worsening vertebral fractures should be explored by modelling and with stratified analyses.

Problems in interpreting results of these studies may arise due to the fact that several efficacy parameters are being analyzed. The protocol should specify one parameter as the primary efficacy variable which will be considered along with the evidence presented from the

remaining (secondary) efficacy variables in making a final determination of efficacy. The evaluation should also include an analysis of the comparability of treatment and control groups at entry into the study with regard to age, race, body weight, smoking history, physical activity, dietary calcium intake, time since menopause, bone density, number of prior fractures, number of normal vertebral bodies at risk, and other identifiable risk factors.

An interim analysis of data prior to completion of the first three years of treatment is discouraged and, if contemplated, should be discussed with the Division.

VI. Safety Testing

The nature and frequency of laboratory and clinical testing to evaluate safety depend in part on the information available from animal studies, the pharmacodynamic and pharmacokinetic data available, and whether there is previous clinical experience with the drug.

Laboratory tests usually performed in the safety evaluation of all drugs include tests of hematopoietic function (hemoglobin, hematocrit, RBC count, WBC count and differential, platelet count), renal function (urinalysis, BUN, creatinine and creatinine clearance), and hepatic function (bilirubin and liver enzymes alkaline phosphatase, 5'nucleotidase, gamma-GPT, SGOT, SGPT, and/or LDH). Other tests that are usually done routinely in a selected number of patients include serum electrolytes (Na, K, Cl, CO_2), plasma glucose, uric acid, serum proteins, prothrombin time and 12-lead electrocardiograph. Complete eye examinations should be done in a representative number of patients.

Because calcium and phosphate metabolism are intimately linked with bone, and agents that affect bone may also affect calcium and phosphate homeostasis, serum levels of these ions should be followed in most cases and urine calcium and phosphate in selected cases. Radiographs and ultrasound to detect soft tissue calcification may also be indicated with certain drugs.

Histomorphometric assessment of bone mineralization defects (for example, after high dose fluoride therapy) and evaluation of bone fragility by an appropriate technique may be helpful in determining whether or not the test drug therapy has any harmful effects on the structure and/or biomechanical strength. For evaluation of safety the bone biopsy and biomechanical strength test should be performed as late in the trial as possible.

VII.

GUIDE TO FDA ACTION on NEW DRUG APPLICATIONS for OSTEOPOROSIS

CLINICAL STUDIES	PRECLINICAL STUDIES (2 Species)	
INCREASED BMD	NORMAL	ABNORMAL
Proven Fracture Efficacy at 3 years	• Approve Drug for Marketing • Phase IV Continuation Not Needed	• Approve Drug for Marketing • Continue Phase IV Open Studies for at least 2 Years
Not Proven Fracture Efficacy at 3 years	• Approve Drug for Marketing • Continue Controlled Studies for 2 More Years	• NO DRUG APPROVAL • Continue Controlled Study for 5 Years to Determine Safety and Fracture Efficacy

VIII. Issues Related to Testing of Combined Drug Regimens

When a drug product contains two or more components in a fixed dosage form, studies must include demonstration of the contribution of each of the ingredients (see 21 CFR 300.50). Evaluating the clinical effectiveness of these drugs entails special considerations because of the difficulties in assessing bone architecture and strength, in vivo. In general, with the exception of calcium, combined drug regimens will need to be tested in trials with multiple treatment arms (i.e., placebo A+ placebo B, Drug A+placebo B, Drug B+ placebo A, and Drug A+ Drug B.

IX. Research Priorities in Postmenopausal Osteoporosis

1. Development of convenient assay methods for routine determination in clinical trials; studying clinical applications of bone-specific biochemical markers in screening patients with postmenopausal osteoporosis and in assessing response to test therapy. The role of biochemical markers in early Phase II dose-ranging studies in adjustment of dosage of the test drug; identifying patients with increased or decreased bone turnover rate. Correlation of changes in biochemical markers with overall changes in skeletal mass.

2. Objective assessment of vertebral deformity; correlation of vertebral deformity index with changes in vertebral bone mineral density and new fractures.

3. Improving the sensitivity and specificity of assessment of prevalent and incident vertebral fractures.

4. Development of techniques for automated assessment of vertebral morphometry.

5. Assessment of bone quality in clinical trials by non-invasive methods.

X. REFERENCES

1. RW Boyce, AF Franks, ML Jankowsky, CM Orcutt, AM Piacquadio, JM White, JA Bevan. Sequential histomorphometric changes in cancellous bone from ovariohysterectomized dogs. J Bone Miner Res 5(9):947-953, 1990.

2. DB Kimmel, RR Recker, JC Gallagher, AS Vaswani, JF Aloia. A comparison of iliac bone histomorphometric data in post-menopausal osteoporotic and normal subjects. Bone and Mineral 11:317-235, 1990.

3. R Baron, R Tross, A Vignery. Evidence of sequential remodeling in rat trabecular bone: morphology, dynamic histomorphometry, and changes during skeletal maturation. Anat Rec 208:137-145, 1984.

4. R Balena, A Markatos, MH Lafage, P Masarachia, M Gentile, GA Rodan. The long term effects of alendronate on bone remodeling in the spine of ovariectomized baboons. J Bone Miner Res (Suppl 1):82A, 1992.

5. K Lundon, M Grynpas. The longterm effect of ovariectomy on the quality and quantity of cortical bone in the young cynomolgus monkey: A comparison of density fractionation and histomorphometric techniques. Bone 14:389-395, 1993.

6. CH Turner, DB Burr. Basic biomechanical measurements of bone: a tutorial. Bone 14: 595-608, 1993.

7. Clinical indications for bone mass measurements. J.Bone Min. Res. 4: (suppl.2),1-28,1988.

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