Osteoporosis: Nonclinical Evaluation of Drugs Intended for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmacology/Toxicology

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I. INTRODUCTION

The purpose of this guidance is to provide recommendations to industry for designing nonclinical studies to support the approval of drugs intended for the treatment of osteoporosis.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the nonclinical development program for biopharmaceuticals to treat osteoporosis.

We recommend sponsors review the following guidances for industry before initiating clinical trials of drugs intended to treat osteoporosis:[3]

- *General Considerations for the Clinical Evaluation of Drugs*
- *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*
- *Study of Drugs Likely to be Used in the Elderly*

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[1] This guidance has been prepared by the Division of Bone, Reproductive, and Urologic Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, *drugs* refers to drug and biological products regulated in CDER.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

In addition to the pharmacology and toxicology studies required for all new drugs,[4] long-term nonclinical pharmacology studies (*bone quality studies*) should be conducted for drugs intended to treat osteoporosis. These studies are warranted because of concerns about long-term adverse effects of pharmaceutical agents on the quality of bone (Harris, Watts, et al. 1993; Kleerekoper 1996; Van der Meulen and Boskey 2012) and because there are no validated and reliable methods for the noninvasive assessment of bone quality in humans. Bone quality refers to those structural and material properties of bone that determine its biomechanical behavior in ways that are not accounted for by bone quantity or mass (Hernandez and Keaveny 2006). Although bone quality cannot be easily assessed directly, nonclinical studies offer the opportunity to provide indirect information about bone quality through the measurement of bone strength, which is determined by both bone mass and bone quality. An adverse effect on bone quality can be identified by a change in the correlation between bone mass (i.e., bone mineral density (BMD) or bone mineral content (BMC)) and bone strength. However, clinical trials must still establish that increases in BMD are associated with reductions in the incidences of bone fractures.[5]

III. NONCLINICAL STUDIES

A. Toxicology Studies

Pharmacology and toxicology studies are needed to support clinical development of new drugs and biologics for osteoporosis indications.[6] In addition to these standard pharmacology and toxicology studies, bone quality studies should be conducted for drugs intended to treat osteoporosis.

B. Bone Quality Studies

1. Animal Species and Models

a. Two-species requirement

Various animal species and models are available for the study of osteoporosis (Turner 2001; Jerome and Peterson 2001). Species and models selected should be relevant to the specific clinical indication for which the drug is being developed. Bone quality studies to support osteoporosis indications generally should be conducted in two different animal species. However, biopharmaceuticals may be exempted from this recommendation (see section III.C., Biopharmaceuticals).

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[4] 21 CFR 312.23(a)(8)

[5] 21 CFR 314.50(d)(2) and 21 CFR 314.50(d)(5)

[6] See the ICH guidances for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals*, *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*, and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.*

b. Osteoporosis models

For postmenopausal osteoporosis, one of the bone quality studies should be conducted in the ovariectomized rat, and the other study should be done in a larger ovariectomized nonrodent species with more extensive cortical remodeling (e.g., nonhuman primate, sheep, pig, or dog). The age of the animals at ovariectomy should be adequate to evaluate the effects of the investigational drug on already formed bone rather than bone growth. Treatment initiation time after ovariectomy should be determined by the intended clinical use of the drug and the expected time course of bone loss in the species used. For other forms of osteoporosis, appropriate animal models (such as the mature orchidectomized rodent for male osteoporosis and the glucocorticoid-treated rabbit for glucocorticoid-induced osteoporosis) and transgenic animal models may provide relevant information (see section III.C., Biopharmaceuticals).

c. Studies to support other osteoporosis indications

When a drug has been approved for a specific osteoporosis indication and the approval was supported by bone quality studies in indication-specific animal models, the nonclinical recommendation to support another osteoporosis indication for the drug may be limited to a short-term study (less than or equal to 6 months) in a relevant animal model that can serve to bridge to the original bone quality studies. The recommendation for additional animal studies depends on the level of scientific concern about the skeletal effects of the drug in other forms of osteoporosis.

2. Study Design

a. Dose selection

Nonclinical bone quality studies generally should be conducted with three doses, including a dose that induces an optimal pharmacological effect on bone mass, a high dose that is an adequate multiple of the optimally effective dose, and a low dose intended to produce a suboptimal response. The optimally effective dose should be determined in dose range-finding studies and should be based on BMD and biochemical markers of bone turnover. The high dose should be used to optimize the identification of adverse bone effects and the low dose can be useful in establishing a no observable adverse effect level for adverse bone effects. The dose selection may be influenced by nonskeletal toxicities.

b. Dosing regimen and administration route

The dosing regimen and administration route in the nonclinical studies should reflect the intended clinical use. Dosing interval should be selected based on the pharmacokinetic profile of the investigational drug and the respective bone remodeling cycle durations in animals and humans. For follow-up indications with different clinical dosing regimens or dose administration routes, the need for additional nonclinical studies should be based on scientific rationale.

c. Study duration

The treatment duration of the long-term bone quality studies should consist of a number of remodeling cycles equivalent to approximately 3 years of human exposure. Assuming that the duration of the bone turnover cycle in humans is 16 to 26 weeks (2 to 3 cycles per year) (Eriksen 2010), approximately 6 weeks in rats (8 cycles per year) (Baron, Tross, et al. 1984) and approximately 10 weeks in monkeys (5 cycles per year) (Schock, Noyes, et al. 1972), a treatment duration of 9 to 14 months in rats and 14 to 22 months in primates would be comparable to approximately 3 years of treatment in humans. Because of their relatively short life-span, studies in rats and mice can be limited to 12 months. In monkeys, a study duration of 16 to 24 months is generally adequate. Study duration also can be affected by other species-specific considerations.

d. Data analysis

Studies should be sufficiently powered to demonstrate statistically significant effects on BMD and biomechanical strength parameters at the optimal dose.

3. Evaluations

a. Bone turnover

Biochemical markers of bone resorption and formation should be measured in the bone quality studies to provide information on bone turnover. Resorption markers include serum or urine cross-linked telopeptides of type I collagen, such as NTx or CTx, and urinary pyridinium cross-links of collagen, such as PYD or DPD. Formation markers include serum OC, PICP, PINP, and BSAP. Data on bone turnover should be collected at interim time points (e.g., at 3, 6, 12, and 18 months) and at end of study. Bone turnover markers do not by themselves provide information on bone quality, but may help to explain or interpret changes in other bone parameters.

b. Bone mass and density

Established noninvasive techniques for the assessment of BMD and BMC, such as dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT), should be used in the bone quality studies. Both axial (spine) and appendicular (long bone) skeletal sites should be examined. The pQCT data should be collected for both cancellous and cortical bone. Geometrical bone properties also should be estimated by densitometric techniques. Ex vivo measurements can be carried out at end of study, but in vivo measurements in anesthetized animals can be performed at interim time points as well.

c. Bone structure and architecture

A qualitative histological evaluation of the microscopic bone structure, with optional histological staining, should be performed to identify bone cell and matrix components. In addition, static and dynamic histomorphometry of cortical and cancellous bone at axial and appendicular skeletal sites should be employed to obtain quantitative information on bone architecture and remodeling dynamics (Parfitt, Drezner, et al. 1987; Dempster, Compston, et al. 2013). Other

imaging or spectroscopic techniques (micro-computed tomography, high-resolution pQCT, magnetic resonance imaging, Raman or infrared spectroscopy, polarized light microscopy, small- and wide-angle X-ray scattering, or advanced forms of computed tomography) can be used to provide additional information on bone structure at different hierarchical levels. Evaluations should be carried out at the end of the study, but data also can be collected at interim time points.

d. Bone strength

Biomechanical testing of both axial and appendicular sites should be performed in the bone quality studies. Tests can include compression tests of vertebrae or vertebral bodies, bending tests of long bones, and femoral neck loading tests. Both extrinsic (e.g., ultimate force, stiffness, work-to-failure) and intrinsic mechanical parameters (e.g., ultimate strength, yield strength, elastic modulus) should be determined (Turner and Burr 1993). Characterization of pre-yield as well as post-yield bone mechanical properties is recommended. The choice of the biomechanical parameter(s) used to describe the bone's mechanical properties and demonstrate an effect of the therapeutic drug should be adequately justified. Geometric and densitometric parameters of the mechanically tested bone types should also be evaluated.

An analysis of the correlation between densitometric parameters (BMC, BMD) and mechanical parameters (e.g., ultimate force, stiffness, work-to-failure, ultimate strength, yield strength, or toughness) is essential and should be carried out to provide information about the value of BMD as a strength predictive parameter for the investigational drug. BMD can be correlated to mass-normalized strength parameters, but BMC should be associated with whole bone (extrinsic) mechanical properties. Importantly, potential differences in the relationship between bone mass and strength parameters between control and treatment groups should be resolved by adequate statistical analysis. Finite element analysis based on computed tomography images can be carried out, but currently is not considered to be a substitute measure of bone strength. Biomechanical assessments should be carried out in animals sacrificed at end of study, but also can be performed in animals sacrificed at interim time points.

e. Additional evaluations

The evaluation of bone quality is a continually evolving field that seeks to characterize bone tissue properties and their relationship to the bone's mechanical behavior using the latest scientific advances. As described above, bone quality is not captured by the measurement of one particular bone parameter but is, in part, reflected by the relationship between specific bone strength and densitometric parameters. Measurement of additional determinants of the bone's mechanical behavior (e.g., fatigue life, fracture toughness, hardness) can be included in animal studies. Other assessments such as histologic evaluation of target organs of toxicity also can be recommended for long-term bone quality studies based on drug- and indication-specific safety concerns. Pharmacokinetic parameters (C_{max}, area under the curve (AUC)) should be evaluated in the bone quality studies to determine human exposure multiples.

Skeletal endpoints in long-term toxicology studies can be used to provide additional nonclinical support for the bone safety and efficacy of therapeutic drugs.

C. Biopharmaceuticals

Biopharmaceuticals (e.g., recombinant proteins and monoclonal antibodies) are typically selected based upon their high specificity for their human target receptor/antigen. This target may be absent in common animal test species, or the nonhuman target (the *ortholog*) may not productively interact with the biopharmaceutical. Species selection for nonclinical bone quality studies of biopharmaceuticals should be guided by pharmacological responsiveness. The test agent should be pharmacologically active in the selected species. The immunogenicity of the biopharmaceutical and the effect of the immune response on systemic exposure, pharmacodynamic response, and toxicity of a drug should be characterized. As a result of these potential limitations, bone quality as well as toxicology studies in a single responsive animal species may be appropriate. In cases where no relevant test species exists, consideration should be given to the use of alternative models, such as the use of an analogous drug (*surrogate*) against the orthologous target, or the use of a transgenic model in which the animal is made to express the human target. For biopharmaceuticals to be used for the treatment of osteoporosis, sponsors should also consult the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

IV. REGULATORY ASPECTS

Sponsors are encouraged to consult with the Division of Bone, Reproductive, and Urologic Products regarding the design of the nonclinical bone quality studies as early in development as possible. Study protocols with detailed description of testing procedures should be submitted for review by the division. Data from dose-range finding studies of relatively short-term duration (3 to 4 months in rodents, 6 months in large animals) can be used to support the initiation of phase 2 or phase 3 clinical trials and inform the design of the long-term studies. Final reports of nonclinical bone quality studies generally should be submitted by the end of phase 3 or at the time of submission of the new drug application or biologics license application. Modification of study timing and requirements can be considered for some drugs according to the level of concern and the availability of relevant animal models. If appropriate, data from short-term dose range-finding studies may be needed to evaluate drug-specific bone safety concerns and support long-term clinical trials.

V. ANABOLIC AGENTS

A toxicological issue for the development of bone anabolic agents for the treatment of osteoporosis is the potential for carcinogenicity. In previous nonclinical studies, rats and mice dosed with parathyroid hormone (PTH) or parathyroid hormone-related peptide (PTHrP) drugs for 4 to 24 months developed bone tumors including osteosarcomas. In rats given daily PTH injections, tumors occurred at low multiples of human exposure (AUC). As a result of the concern about carcinogenicity, studies to evaluate carcinogenic potential generally should be conducted with PTH drugs developed for the treatment of osteoporosis. Relevant drugs include PTH- and PTHrP-related peptides and other drugs stimulating osteoblastic bone formation.

These studies may entail unique design features. Therefore, study protocols should be discussed with the division before study initiation.

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