Osteoporosis: Nonclinical Evaluation of Drugs Intended for Treatment

Guidance for Industry

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

August 2019
Pharmacology/Toxicology

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I. INTRODUCTION

The purpose of this guidance is to provide recommendations to industry for designing nonclinical bone quality studies to support the approval of drugs and biologics intended for the treatment of osteoporosis.[2]

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* (January 1997)
- *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)
- *Study of Drugs Likely to be Used in the Elderly* (November 1989)

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Bone, Reproductive, and Urologic Products in the Center for Drug Evaluation and Research 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 https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

II. BACKGROUND

In addition to the pharmacology and toxicology studies required for all new drugs,[4,5] long-term nonclinical studies to evaluate bone tissue (*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 bone quality (Harris et al. 1993; Kleerekoper and Vieth 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). An adverse effect on bone quality can be identified by an unfavorable change in the correlation between bone mass (i.e., bone mineral density (BMD) or bone mineral content (BMC)) and bone strength. The nonclinical bone quality studies are intended to evaluate this correlation and can provide support for the validity of BMD as a surrogate marker for fracture risk in clinical studies. However, increases in BMD and reductions in the incidences of bone fractures must still be established in clinical trials.[6]

III. NONCLINICAL STUDIES

A. Toxicology Studies

Pharmacology and toxicology studies are needed to support clinical development of new drugs and biologics for osteoporosis indications.[7] In addition to conducting these standard pharmacology and toxicology studies, the sponsor should conduct nonclinical bone quality studies for drugs intended to treat osteoporosis.

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

[5] See the ICH guidances for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals* (July 2001), *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), and *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012).

[6] 21 CFR 314.50(d)(2) and 21 CFR 314.50(d)(5)

[7] 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. Bone Quality Studies

1. General

a. Animal models[8]

Various animal models are available for the study of osteoporosis (Turner 2001; Jerome and Peterson 2001). For the bone quality studies, the sponsor should select osteoporosis models that are relevant to the specific clinical indication for which the drug is being developed. For postmenopausal osteoporosis, bone quality studies should be conducted in ovariectomized animals. 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., Biologics).

b. Animal species

Generally, the sponsor should conduct bone quality studies in two animal species. For postmenopausal osteoporosis, one of the studies should be conducted in the ovariectomized rat. Generally, a study in a larger ovariectomized nonrodent species with more extensive cortical remodeling (e.g., nonhuman primate, sheep, pig, or dog) should also be conducted. For other osteoporosis indications, one bone quality study should be conducted in rodents and another in an appropriate animal model for the intended indication. Biologics may be exempted from the two-species recommendation (see section III. C., Biologics).

c. Osteoporosis indications

When a drug has been approved for a specific osteoporosis indication supported by bone quality studies in indication-specific animal models, the need for additional nonclinical studies to support another osteoporosis indication depends on the concern about the skeletal safety of the drug in the other form of osteoporosis. The recommended evaluation may be limited to a relatively short-term study in a relevant animal model that can serve as a bridge to the original bone quality studies. Additional animal studies to support osteoporosis indications involving combination drug treatments may also be needed depending on the level of scientific concern.

2. Study Design

a. Dose selection

The sponsor should generally conduct the bone quality studies with at minimum two doses, including a dose that induces an optimal pharmacological effect on bone mass and a high dose that is an adequate multiple of the optimally effective dose. An optional low dose can be useful

[8] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. The FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. The FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

for determining dose-effect relationships. Dose selection should be determined in dose range-finding studies. The optimal dose should be based on BMD and biochemical markers of bone turnover and the high dose should be selected to identify adverse bone effects. The dose selection may be influenced by nonskeletal toxicities.

b. Dosing regimen and administration route

The dosing regimen and route of administration should reflect the intended clinical use. Dosing intervals should be selected on the basis of 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 routes of administration, the need for additional nonclinical studies should be based on scientific rationale.

c. Treatment initiation and duration

The sponsor should determine treatment initiation time (e.g., after ovariectomy) based on the intended clinical use of the drug. The animal's age during treatment should be adequate to ensure the evaluation of the drug's effects on already-formed bone rather than bone growth (i.e., animals should be skeletally mature). The sponsor should determine treatment duration based on the intended clinical treatment duration and the bone remodeling cycle duration in the species studied. For example, assuming the duration of the bone turnover cycle is 120 days to 200 days in humans (Eriksen 2010), 40 days in rats (Baron et al. 1984), and 75 days in monkeys (Schock et al. 1972), a study duration of 7 to 12 months in the rat and 14 to 23 months in the monkey would be adequate to support at least 3 years of human exposure. Study duration also can be affected by other species-specific considerations, such as the age of the animals at treatment initiation. The sponsor should consider the use of relevant nonrodent models other than monkeys. The sponsor should discuss the timing and design of the long-term bone quality studies with the division, as early in development as possible (see section IV, Regulatory Aspects).

d. Data analysis

Studies should be sufficiently powered to demonstrate statistically significant effects on BMD and biomechanical strength parameters at the optimal dose. Group sizes for rats of 20 to 25 per group and group sizes for larger animals of 10 to15 per group are generally adequate.

3. Evaluations

a. Bone turnover

The sponsor should measure biochemical markers of bone resorption and formation in the bone quality studies to provide information on bone turnover. Bone resorption markers include serum or urine cross-linked telopeptides of type I collagen, such as collagen type I cross-linked N-telopeptide (NTx) or collagen type I cross-linked C-telopeptide (CTx), and urinary pyridinium cross-links of collagen, such as pyridinoline (PYD) or deoxypyridinoline (DPD). Bone formation markers include serum osteocalcin (OC), procollagen type I C-terminal propeptide

(PICP), procollagen type I N-terminal propeptide (PINP), and bone-specific alkaline phosphatase (BSAP). Data on bone turnover should be collected at interim time points (e.g., at 3, 6, 12, and 18 months) and at the end of the 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

The sponsor should use established noninvasive techniques for the assessment of BMD and BMC, such as dual energy X-ray absorptiometry and peripheral quantitative computed tomography (pQCT), 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 using densitometric techniques. Ex vivo measurements can be carried out at end of study, but in vivo densitometric measurements in anesthetized animals can be performed at interim time points.

c. Bone structure and architecture

The sponsor should perform a qualitative histological evaluation of the microscopic bone structure, with optional histological staining, to identify bone cell and matrix components. In addition, the sponsor should employ static and dynamic histomorphometry of cortical and cancellous bone at axial and appendicular skeletal sites to obtain quantitative information on bone architecture and remodeling dynamics (Parfitt et al. 1987; Dempster et al. 2013). Other imaging or spectroscopic techniques (microcomputed 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

The sponsor should perform biomechanical testing of both axial and appendicular sites 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 (e.g., ultimate strength, yield strength, elastic modulus) mechanical parameters should be determined (Turner and Burr 1993). Characterization of pre-yield as well as post-yield bone mechanical properties is recommended. The sponsor should justify the choice of the biomechanical parameter or parameters used both to describe the bone's mechanical properties and to demonstrate an effect of the therapeutic drug. 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, the sponsor should determine potential differences in the relationship between bone mass and strength parameters between control and treatment groups by adequate statistical analysis. Finite element analysis based on computed tomography images can be carried out, but finite element analysis is currently not considered to be a substitute measure of bone strength. Biomechanical assessments should be carried out in animals sacrificed at the end of the study but also can be performed in animals sacrificed at interim time points.

e. Additional evaluations

Bone quality evaluation 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 mechanical and densitometric parameters. The sponsor can include measurement of additional bone mechanical properties (e.g., fatigue life, fracture toughness, hardness) in the animal studies.

In addition to the evaluation of skeletal effects, bone quality studies may be suitable for toxicological assessments based on drug- and indication-specific safety concerns and as appropriate for the animal model utilized. This could include measurement of standard toxicological parameters as well as histologic evaluation of target organs of toxicity. The sponsor should evaluate pharmacokinetic parameters (C_{max}, area under the curve (AUC)) in the bone quality studies to determine human exposure multiples.

Skeletal endpoints in long-term toxicology studies may also serve to provide additional nonclinical support for the bone safety and efficacy of therapeutic drugs.

C. Biologics

Biologics (e.g., recombinant proteins and monoclonal antibodies) are typically selected on the basis of their high specificity for their human target receptor or antigen. This target may be absent in common animal test species, or the nonhuman target (the *ortholog*) may not optimally interact with the biologic. Because of these potential limitations, it may be appropriate to conduct bone quality studies as well as toxicology studies in a single pharmacologically responsive animal species. The sponsor should characterize the immunogenicity of the biologic and the effect of the immune response on systemic exposure, pharmacodynamic response, and toxicity of the drug. In cases where no relevant test species exists, the sponsor should consider 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 biologics to be used for the treatment of osteoporosis, the sponsor should also consult the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.*

D. Anabolic Agents

A toxicological issue for the development of bone anabolic agents for the treatment of osteoporosis is the potential for carcinogenicity due to osteoblast stimulation. 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, at low multiples of human exposure (AUC). Because carcinogenicity studies with anabolic agents may entail unique design features, the sponsor should submit study protocols for review by both the Division of Bone, Reproductive, and Urologic Products and the Executive Carcinogenicity Assessment Committee (ECAC) before study initiation.

IV. REGULATORY ASPECTS

The sponsor is encouraged to consult with the division regarding the conduct and design of the bone quality studies as early in development as possible. Study protocols with a detailed description of testing procedures should be submitted for review by the division. Data from dose-range finding studies of relatively short-term duration (e.g., 3 months in rodents, 6 months in large animals) may be needed to evaluate drug-specific bone safety concerns, support the initiation of phase 2 or phase 3 clinical trials, and inform the design of the long-term studies. The sponsor should submit study reports of the bone quality studies by the end of phase 3 or at the time of submission of the new drug application or biologics license application. For some drugs, the sponsor may consider modifications of the study program, including extent of studies, study timing, and study design, based on toxicological or clinical safety concerns or the available relevant animal models.

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