



GlaxoSmithKline

7 April, 2004

1226 04 APR -7 '04 123

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

GlaxoSmithKline
2301 Renaissance Boulevard
P.O. Box 61540
King of Prussia, PA
19406-2772
Tel 610 787 7000
Fax 610 787 7777
www.gsk.com

**Re: Comments on Draft Guidance for Industry on the Preclinical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

Dear Sir or Madam::

Reference is made to the Agency's request for comments on the subject draft guidance, published in the *Federal Register* on February 11, 2004, Vol. 69, No. 28, pages 6673-6674 (Docket No. 2004D-0035).

GlaxoSmithKline welcomes the Agency's initiative to solicit input in preparation for updating this draft guidance to industry, and therefore is pleased to enclose a document responding to this request for comments.

Please note that in addition to the two specific points on which the Agency has solicited input, the comments contained herein also address other aspects of the guidance we believe should be reviewed in the context of learnings in this therapeutic area since the last update in 1994.

These comments along with supporting published references are provided in duplicate; an electronic copy is also enclosed. If you have any questions regarding these comments, please do not hesitate to contact me at (610) 787-3727.

Sincerely yours,

Richard Phillips, Executive Director
CEDD Global Regulatory Affairs

2004D-0035

C1

COMMENTS ON: DRAFT GUIDANCE FOR INDUSTRY ON THE PRECLINICAL AND CLINICAL EVALUATION OF AGENTS USED IN THE PREVENTION OR TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

[DOCKET NO. 2004D-0035]

FEDERAL REGISTER NOTICE 11TH FEBRUARY, 2004

OVERALL COMMENTS

GlaxoSmithKline welcomes the Agency's initiative to solicit comments in preparation for updating this draft guidance to industry.

There has been considerable progress in our understanding of the osteoporosis disease process since the guidance was last updated, and associated learnings regarding approaches to developing safe and effective therapies.

In addition to the two specific points on which the Agency has solicited input, the comments contained herein address other aspects of the guidance we believe should be reviewed in the context of learnings in this area since the last update.

COMMENTS ON ASPECTS IDENTIFIED IN THE FEDERAL REGISTER REQUEST FOR COMMENTS:

1) Is it appropriate to continue to use placebo controls in fracture trials?

GSK supports maintaining the existing provision in the guideline for performing randomized placebo (i.e. supplemental Vitamin D and calcium) controlled clinical trials in properly defined populations to assess the safety and efficacy of new pharmacological agents for the prevention and treatment of postmenopausal osteoporosis.

We recognize that the availability of additional safe and effective therapies for osteoporosis has changed the clinical research environment, and that following the year 2000 update of the Declaration of Helsinki, there is an on-going dialog among stakeholders regarding the ethics of placebo controlled fracture trials for osteoporosis.

However proposed alternatives such as the option of conducting placebo controlled trials in patients at low risk of fracture or active controlled equivalence or non-inferiority fracture trials carry their own limitations.

Placebo controlled fracture studies conducted in patients at low risk of fracture (e.g. patients with low BMD and no prevalent fractures) would require large numbers of patients to demonstrate a reduction in fracture risk.

Such a study would also have ethical issues, as most of these patients could anticipate little benefit in terms of fracture risk reduction, but would still be exposed to the same level of potential risk of treatment-related adverse events as women at higher fracture risk.

There would also remain the question of whether risk:benefit ratios observed in this low risk population would apply to patient populations at higher risk of fractures, and thus more likely to be treated with a new agent in clinical practice.

Another alternative to placebo controlled trials are active controlled equivalence or non-inferiority trials with fracture endpoints. As well documented in the literature, such studies would require substantially larger sample sizes than placebo controlled superiority trials, and hence would impose a much greater burden of study-related fractures on the study population than superiority studies employing a placebo (calcium / Vitamin D) control arm.¹

In addition, the choice of the active comparative drug and the margin for demonstrating equivalence or non-inferiority should reflect what is considered clinically relevant, but consensus may be difficult to achieve, given the variance in effect size of approved therapies across studies. Related to this, internal or external study validation required to allow unambiguous interpretation also could be problematic in the case of active controlled fracture trials testing an equivalence or non-inferiority hypothesis.

Finally the time, cost and investigative resources required to conduct non-inferiority or equivalency studies would be of a magnitude that may discourage sponsors from continuing to invest in this area, and thus stifle development of new therapies potentially having an improved benefit:risk ratio.

However in order to address the issues alluded to above, GSK is recommending that the current guidance document be revised to allow for demonstration of efficacy in placebo controlled fracture trials of substantially shorter duration than the current three to five years cited in the guideline. See our response to question 2 below for specifics of this proposal.

2) Do fracture trials need to be 3 years in duration, or could shorter trials provide adequate evidence of safety and effectiveness?

We believe that the now considerable body of experience in developing multiple classes of drugs to treat postmenopausal osteoporosis supports the conclusion that phase III clinical trials of shorter than 3 years in duration, i.e. one to two years, in the context of the overall preclinical and clinical program, can provide adequate evidence of safety and effectiveness, sufficient to support risk:benefit assessments for approval purposes.

Efficacy: As has been demonstrated in trials with both anti-resorptive² and bone-building³ agents, a definitive effect on a fracture endpoint can be demonstrated in appropriately designed trials of one to two years in duration. Thus there is ample precedent for

concluding that fracture trials of less than 3 year duration can provide adequate evidence of effectiveness in reducing fracture risk.

While we recognize there have been instances where positive effects on bone and fracture risk observed in the first one to two years of treatment were later lost, assessing bone quality in preclinical studies, coupled with continued assessment of women entered in long term extension studies and an appropriate post-marketing benefit:risk assessment activities can mitigate the risk that an initial beneficial effect is later lost or reversed.

We also recommend that the guidance allow the option for patients to be switched to an active treatment while remaining in the study after the occurrence of a first incident fracture. This would address potential ethical issues based on evidence that an average of 20% of patients experiencing an incident vertebral fracture will experience a subsequent fracture within 12 months following their first fracture⁴.

Safety: We believe that the scenario described above for assessment of efficacy, i.e. one to two year phase 3 trials, with provision for patients to enter long term extension studies, and supported by preclinical bone quality studies, would provide an adequate assessment of safety.

This is predicated on the assumption that preclinical bone quality studies and bone biopsies obtained from women in phase III and extension trials evidence no cause for concern in this regard, and that post-marketing benefit:risk assessment activities are tailored to the particular drug / drug class.

Experience in this therapeutic area suggests that such a clinical development program would result in a safety database exceeding the minimum targets established by ICH Guideline E1A⁵, i.e. a total exposure of approximately 1500 patients, with 300-600 treated for six months, and a minimum of 100 for one year.

Also partial reliance on preclinical studies to address potential longer term deleterious effects on bone quality is consistent with ICH E1A, specifically item 7.a, although data from women enrolled in extension studies along with post-marketing surveillance would also factor into addressing this concern.

COMMENTS ON ADDITIONAL ASPECTS BEYOND THOSE IDENTIFIED IN THE FEDERAL REGISTER REQUEST FOR COMMENTS:

Scope of the Guidance Document:

We believe it would be helpful if the postmenopausal osteoporosis guidance were extended to cover osteoporosis of differing etiologies, e.g. steroid-induced and male osteoporosis. While there is precedent provided by the development and regulatory histories of agents

approved for such indications, it would be helpful to sponsors if specific guidance could be provided in these indications.

Related to this we recommend that the guidance specifically allow for one of these related indications to form the basis for the initial approval of a new agent, provided a fracture effect is demonstrated.

We also recommend that the agency describe in the guideline what we understand to be a policy of allowing for approval of "product enhancements" (e.g. revised doses, formulations, dosing regimens) on the basis of bone mineral density (BMD), provided that a fracture effect has been demonstrated previously.

We recommend further consideration be given to instances where it may be appropriate to modify the requirements for approval of different drug classes or mechanisms of action, in a fashion similar to the distinction made for estrogens in the current guideline.

Relating to the above, we recommend the Agency's draft guideline, Development of Parathyroid Hormone for the Prevention and Treatment of Osteoporosis, issued for comment in May, 2000, be incorporated into this guidance document, rather than constituting a stand-alone guidance specific to this single agent.

Guidance Section "Preclinical Evaluation":

We have several comments and recommendations for consideration for revising this section of the guidance dealing with preclinical bone quality studies.

The guidance states that effects of a drug on bone quality be evaluated in two species, one being the ovariectomized rat and the second, a non-rodent species with Haversian remodeling. The key purpose of bone safety studies is to permit early identification of drugs that result in abnormal architecture and cause a dissociation of relationship of mass and strength. Following are our comments and recommendations relating this aspect of the guidance.

Clarification of the requirement for a dose 5-fold higher than the pharmacological dose would be helpful.

It is unclear whether this requirement is based on systemic exposure multiple or nominal administered dose, and what consideration needs to be given to clinical exposure for dose selection in bone quality studies; it would be helpful if this were clarified in the guidance.

We recommend the requirement for ovariectomy in non-rodent species be reconsidered.

Because the ovariectomized rat is an accepted model for cancellous bone changes in human, a major focus of bone safety studies in non-rodent species is to determine potential deleterious effects of a drug on cortical bone.

However the requirement for ovariectomy in the non-rodent species seems unnecessary as its effects on cortical bone are minimal in the timeframe studies are typically conducted

(16 months). Furthermore, it does not model the cortical osteopenia of osteoporosis of diverse etiology, including estrogen deficiency, corticosteroid-induced, or aging. Assessment of drugs in a skeletally mature intact non-rodent species can identify potentially deleterious effects on cortical and cancellous bone and provide a basis for assessment of risk to the osteoporotic skeleton.

We recommend that the guidance recognize the utility of the dog as a model for assessing bone-active agents.

The dog does not display estrogen-deficiency related cancellous bone loss, and would not be an appropriate model to evaluate effects of estrogen or estrogen like drugs on cancellous bone loss.

However, because of its extensive remodeling-based skeleton, the dog has been used extensively in skeletal research to characterize effects of bone-active agents on remodeling kinetics and envelope-specific behavior that impact mass and architecture of cancellous and cortical bone. Where human data are available, the dog has largely predicted human response. Therefore, the utility of the dog as an animal model should not be underestimated. Its usefulness in examining skeletal effects and safety of bone-active agents, particularly new classes of anabolic agents, should be reconsidered, and recognized in the guidance.

We recommend that guidance on study duration be reconsidered.

The guidance states study design should be reflective of clinical indication. For anabolic agents to be used to treat severe osteoporosis, an intervention design would be most appropriate.

The most appropriate rodent model for this study design initiates treatment several months post-ovariectomy (e.g. 6 months) where a substantial loss of cancellous bone has occurred and accelerated bone turnover has abated. In such a design, rats would be ~9 months of age at the time of initiation of treatment. The requirement for 1 year of treatment in these osteopenic rats results in studies that become confounded by age-related pathologies.

We recommend the Agency consider modifying the requirement in intervention study designs to 6 months treatment, particularly with agents that increase turnover, thus increasing the number of modeling/remodeling events occurring during drug treatment. Also, the Agency may find in reviewing rodent prevention studies with 6 month vs. 1 year treatment durations that perhaps the additional 6 months of treatment adds little value in detecting deleterious effects on bone quality.

In the current guidelines, the duration of *non-rodent* studies appears to have been based on active remodeling times in human to estimate turnover as 2-4 cycles/yr. We believe that activation frequency may be a more suitable comparative index because it estimates frequency of remodeling events.

The Agency could consider estimating turnover in human based on data from recent clinical trials in postmenopausal women. Histomorphometric analyses from these studies report activation frequency estimates of approximately 0.25 to 0.5/yr (i.e. 100% cancellous bone surface remodels 1 to 2 times in 4 years). This could have consequences on study duration requirements for certain non-rodent species such as dog. Treatment duration for an equivalent number of remodeling events on cancellous bone surfaces would be 7 to 16 months (AcF 1.5-1.7/yr) in adult skeletally mature dogs.

We recommend the guidance be modified to permit capture of bone safety endpoints in chronic canine toxicology study rather than in separate 'bone quality studies'.

If the dog is determined to be a suitable species to assess bone safety of a particular drug, bone safety endpoints could be captured in one year chronic toxicology studies. The frequency of cancellous bone remodeling is reported to be 1.5 –1.7/yr in young adult skeletally mature beagle dogs. Hence in a 1 year study, the number of remodeling events is essentially equivalent to 4 years in a postmenopausal osteoporotic population.

Expanding 1 year chronic dog studies to include bone safety endpoints would identify potential deleterious effects on the skeleton i.e. abnormal architecture and a dissociation of mass and biomechanical competence, and would be better designed to characterize a possible dose-response.

In cases where the monkey is the selected species for chronic toxicology studies, the same approach could be applied if skeletally mature monkeys were used.

Incorporating bone safety into the chronic toxicology studies would reduce cost, time, and animal use, and provide bone safety data prior to Phase III.

We suggest the Agency consider modifying the guidance to encourage sponsors to propose a plan detailing a strategy to evaluate bone safety on a case-by-case basis.

This plan would be directed by knowledge of mechanism of action and intended clinical use of the specific agent. It would be formulated with sound scientific justification and include robust endpoints. As suggested above, the plan could potentially include capturing bone safety endpoints in chronic toxicology studies where safety margins could be delineated.

We recommend the biochemical markers and imaging modalities cited in the preclinical section of the guidance be updated.

Specific recommendations reflecting progress in the area of biomarkers and imaging since the guidance was last updated are found below, in comments relating to similar guidance for clinical studies.

Guidance Section "Clinical Evaluation":

II. Clinical Studies:

B. Phase II Studies:

We have several recommendations for revising this section of the guidance.

The guideline states that Phase II studies should be one year in duration, and employ BMD as the primary endpoint. We recommend that allowance be made for use of endpoints other than BMD, since it may be feasible to base phase III dose selection on an endpoint other than BMD, e.g. bone biomarkers, or there may be better predictors of fracture benefit for certain classes of drugs.

In addition, we recommend that allowance be made for Phase II studies of less than one year duration. Depending on the endpoint and the magnitude of the treatment effect of the compound, it may well be possible to generate data sufficient to select phase III doses in studies of less than one year duration.

Also see comments under V. Statistical Considerations, below regarding the potential use of "adaptive / seamless" study designs.

We recommend that the list of biomarkers identified for studying the pharmacodynamic actions of a drug (guidance document page 8) be updated to include those commonly accepted and used, e.g. to include:

- Serum and/or urine C- and N- telopeptides of Type I Collagen (CTX and NTX respectively) as resorption markers.
- Serum osteocalcin, bone-specific alkaline phosphatase, and serum and/or urine C- and N- telopeptides of Type I procollagen (P1CP and P1NP respectively) as formation markers.

C. Phase III Studies:

1. Drugs for Treatment of Patients with [Established] Osteoporosis:

We recommend the term "established" be deleted from the guidance.

This term is not consistent with terminology used in the labeling of products approved for treatment of postmenopausal osteoporosis.

a) Study Design:

We propose that this section of the guideline be reworded to place equal emphasis on the potential to test a non-inferiority hypothesis in an active controlled fracture trial.

The current wording of this section could be read to suggest that studies employing an active control should by default test a superiority rather than a non-inferiority hypothesis.

While this may have been a reasonable position when the guideline was last updated in the context of the limited therapies available at that time, we have subsequently seen the introduction of drugs with a significantly enhanced effect on fracture risk reduction.

The need to demonstrate superiority to these newer agents in fracture risk reduction presents a substantial hurdle to innovation and market entry for newer therapies, which may in fact offer advantages to patients in aspects other than fracture risk reduction, e.g. safety, tolerability, convenience, etc.

Guidance on considerations relating to non-inferiority trial design and data analysis, including considerations relating to choice of comparator agents, acceptable non-inferiority margins, etc. would also be helpful.

b) Study Population:

We recommend that the patient inclusion criterion for lumbar spine BMD be revised from "> 2 S.D. below the mean peak BMD for premenopausal women" to "a lumbar spine T-score of < -2.5", to be consistent with populations enrolled in treatment trials forming the basis for approval of current therapies.

2. Drugs for Prevention of Bone Loss in Asymptomatic Patients:

a) Study Design:

We recommend that the division accept a study duration of 12 to 18 months, vs. the current recommendation of two years.

Although the placebo-corrected changes in BMD observed in the prevention population are less pronounced than in the treatment population, the differences in treated vs. placebo patients are evident at six months and maintained throughout the two-year study period. A 12 to 18 month study would meet or exceed the minimum targets established by ICH guidelines for safety and would be an integral part of the entire safety package.

b) Study Population:

We recommend that the guidance be revised, such that the study population for prevention studies is defined as including women who have been postmenopausal for at least one year [vs. the current one to three years, and without the age > 45 years criterion], and who do not have an osteoporosis-related vertebral fracture and who have a lumbar spine BMD T-score of > -2.5.

This would allow the population in prevention trials to represent more closely the population actually treated in clinical practice.

III. Study Duration and Assessment of Efficacy:

As currently worded, this section anticipates that fracture trials will be 3 to 5 years in duration; as per our response to the Agency's specific question on study duration, we

believe that studies of a shorter duration, coupled with supportive preclinical and clinical studies, can provide adequate evidence of safety and effectiveness.

A. Evaluating Skeletal Mass / B. Other Measurements:

We anticipate that the Agency will update these sections of the guidance to reflect the considerable advances in these areas since the last update in 1994.

Additional imaging modalities would include volumetric quantitative CT scanning, high-resolution CT scanning, micro-CT and micro-MRI, and trabecular architecture from plain films.

For bone biopsies, synchrotron micro-CT scan analysis of bone biopsy material should be considered.

V. Statistical Considerations:

We have several recommendations for revising this section of the guidance.

As an alternative to traditional trial designs, we recommend the guideline allow for use of novel "adaptive / seamless" design studies, if appropriate to the circumstances of the agent under development.

These designs have the potential to increase accuracy in decision making by adapting the design (e.g. dropping dose groups, increasing cohort size) while the study is on-going, based on prespecified interim data analyses and decision making rules. Use of such novel designs could potentially obviate the need for discrete phase II and phase III studies, thereby shortening overall development time.

We believe that once the sponsor has conclusively demonstrated a reduction in vertebral fracture risk as a primary endpoint, a lower statistical hurdle (e.g. alpha level of 0.10) would be appropriate for demonstrating an effect on secondary fracture endpoints at sites with lower incidence rates such as non vertebral / hip fracture, if effects on accepted surrogate markers support a beneficial effect on fracture risk at those sites.

We recommend the guideline allow for use of a repeated measures analysis technique, to take advantage of more than one measurement / data point for a parameter (e.g. biomarkers and/or BMD), where appropriate. Also, regarding the analysis of fracture endpoints, the guidance should allow for a time-to-event approach.

Interim analyses should not be discouraged as they can help the sponsor in making decisions which would benefit the study population, e.g. as suggested in the earlier comments on adaptive / seamless study designs.

Since combination therapy is currently being clinically evaluated for osteoporosis (including both concomitant or sequential administration of agents), we recommend the guideline identify factorial study designs as a way to more fully understand the effects of

combinations of factors (i.e. treatments), which will help to identify optimal combination therapies.

VII. Guide to FDA Action on NDA for Osteoporosis:

We believe that this section should be revised to allow greater flexibility with respect to phase III study duration.

Consistent with our comments on the Agency's question regarding the adequacy of studies of less than three years duration to provide evidence of safety and efficacy, we believe this section should be revised to eliminate the categorical reliance on three or five year studies. Greater flexibility in making risk:benefit assessments should be allowed, integrating data from preclinical studies, phase III and extension trials, and the sponsor's post marketing benefit:risk assessment activities, also taking into consideration the specifics of the agent / class under consideration.

VIII. Issues Related to Testing of Combined Drug Regimens:

We encourage the Agency to give careful consideration to updating and expanding this section of the guidance, given the number of new agents and classes which have entered the market since the last update, and the keen interest in the potential benefits of combined or sequential use of agents with complementary mechanisms.

Specifically, we encourage the Agency to expand the guidance beyond fixed dose combinations to cover co-administration of a marketed agent with a new experimental therapy, including allowance for initial approval on the basis of demonstrating an additive effect for fracture, but without the single agent needing to be demonstrated efficacious when used as a single agent on its own.

It would also be useful if the guidance could be expanded to cover sequential (vs. concomitant) use of agents, as now being explored in trials of anti-resorptive and bone-building agents, e.g. considerations for trial design, type of indications / labeling claims which might be supported, etc.

For example, would the Agency consider approving an anti-resorptive agent for use to maintain increased bone resulting from a course of a bone building agent, without requiring an effect be demonstrated on fracture risk?

References:

¹ Kanis et al, Uncertain Future of Trials in Osteoporosis, *Osteoporosis Int* 2002; 13:443-449

² Harris, ST, et al., Effects of Risedronate on Vertebral and Nonvertebral Fractures in Women with Postmenopausal Osteoporosis: A Randomized Controlled Trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group, *JAMA* 1999; 282(14): 1344-52.

³ Neer, RM, et al., Effect of Parathyroid Hormone (1-34) on Fractures and Bone Mineral Density in Postmenopausal Women with Osteoporosis. *N Engl J Med* 2001; 344(19): 1434-41.

⁴ Lindsay, R et al, Risk of New Vertebral Fracture in the Year Following a Fracture, *JAMA* 2001; 285(3): 320-323.

⁵ Guideline for Industry, ICH-E1A, The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions, March, 1995
