GlaxoSmithKline Proposal for Amending the FDA Guideline For Evaluation of Postmenopausaul Osteoporosis Therapies

Introduction:

The purpose of this document is to respond to the solicitation of written comments on design of clinical trials of new osteoporosis treatments published in the **Federal Register**, Vol. 67, no. 148, on August 1, 2002.

There are now a number of drugs widely available to patients and physicians for the treatment of osteoporosis. The primary mechanism of action of these drugs is to inhibit bone resorption; thus there is still a remaining unmet need for new and alternative therapies which could also stimulate bone formation.

The basis of approval for the currently marketed drugs has been the FDA Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis (April, 1994).

Consequently, approval of current agents for the treatment of osteoporosis was obtained after the demonstration of their efficacy in reducing fracture risk, usually vertebral fractures (1, 3, 4), in 3 year placebo controlled Randomized Clinical Trials (RCT's), combined with the demonstration that these agents had no detrimental effect on bone quality in preclinical studies.

Problem Statement:

Several observations can be made from the drug approvals granted for the treatment of osteoporosis over the past several years.

- Preclinical rodent and non rodent animal models have shown a strong predictive value to assess the effect of new agents on bone quality during chronic therapy.
- Publication of the results of several placebo controlled RCT over the past several years has also shown that it is possible to demonstrate a significant vertebral fracture risk reduction within 12 to 18 months in studies with patients at high risk of fractures and the appropriate sample size. This was shown with an antiresorptive agent (risedronate) (4, 5) as well as with a bone forming agent (PTH) (6). In addition, the PTH study has also shown a significant effect on non vertebral fracture risk reduction within 18 months of therapy.

- A specific reduction of hip fracture risk has only been shown in patients or subgroups of patients at high risk of such fractures (i.e. patients with low femoral neck BMD and prevalent vertebral fractures) (1, 7). Even though these studies enrolled thousands of patients at high risk of hip fractures, the observed yearly incidence of hip fractures remained very low during the duration of the studies, whereas a large proportion of patients, especially in the placebo group, suffered from incident vertebral and non vertebral fractures leading to an aggravated morbidity of the study population.
- The availability of effective therapies for osteoporosis has changed the clinical research environment, and following the year 2000 update of the Declaration of Helsinki, institutional review boards, physicians and informed patients are now questioning the ethics of placebo controlled trials for osteoporosis.

Hence, revised regulatory guidelines need to reflect the ethics and feasibility of placebo controlled RCT's in the treatment of osteoporosis.

Discussion:

Multiple channels of debate have been ongoing recently relating to the apparent contradiction between current regulatory guidelines and the ethics and feasibility of conducting large and lengthy placebo controlled RCT's in osteoporosis.

Alternatives to placebo controlled RCT's like equivalence or non- inferiority trials have been considered in this debate, as well as the option of conducting placebo controlled RCT's in patients at low risk of fractures (8, 9). But these alternatives carry their own limitations:

- Equivalence or non-inferiority trials with fracture endpoints would require even larger sample sizes than placebo controlled RCT's and hence would impose a greater burden of study-related fractures on the study population. In addition the choice of the active comparative drug and the margin for demonstrating equivalence or non-inferiority in these trials should reflect what is considered clinically relevant but may

become very controversial. Finally the resources required to conduct such studies would be of a magnitude which could discourage continued research in this area.

- Placebo controlled fracture studies conducted in patients at lower risk of fracture (i.e. patients with low BMD and absence of prevalent fractures) would also require large numbers of patients to demonstrate a reduction in fracture risk. Most of these patients would have little benefit to expect in terms of fracture risk reduction during the trial, but would still be exposed to the potential risk related to treatment-related adverse events. Consequently benefit risk ratios observed in this low risk population may not apply to patient populations at high risk of fractures.

Proposals:

GSK supports maintaining the existing requirement for placebo controlled RCT's to demonstrate the efficacy of new pharmacological agents for the treatment of postmenopausal osteoporosis.

Nevertheless GSK is suggesting the following changes to the existing guidelines:

- If adequate preclinical bone quality studies have demonstrated that a new pharmacological agent does not compromise bone quality, the duration of placebo controlled RCT's to demonstrate reduction in vertebral and non vertebral fracture risk could be reduced to that required to demonstrate efficacy, e.g. from 3 years to 18 months. In addition, allowance should be made in guidance to allow the option of conducting these studies using a time to first event / fracture statistical analysis and allowing patients to be switched to an active treatment while remaining in the study after the occurrence of a first incident fracture. This would be ethically justified as it has been shown that an average of 20% of patients having experienced an incident vertebral fracture will suffer from a subsequent fracture within 12 months following their first fracture (10).
- If the efficacy of a new pharmacological agent to reduce the risk of vertebral and non vertebral fractures has been appropriately demonstrated, a specific indication for reduction in risk of hip fracture could be obtained based on the outcome of a study

designed with BMD endpoint versus an active control approved for the hip fracture indication.

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