GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS

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1. INTRODUCTION

This guidance is intended to recommend clinical trials and clinical drug development programs that will provide acceptable demonstrations of the safety and efficacy of drugs to improve health and self-esteem by reducing body fat. General guidelines for conduct of clinical trials and for development of new drugs for marketing should be followed in developing weight-control drugs. Only those aspects of the trials that are specific to weight-control drugs will be discussed in this document. Refer particularly to the Guidelines for the Format and Content of the Clinical and Statistical Sections of New Drug Applications.

2. GENERAL RATIONALE

Excess weight is associated with excess morbidity (diabetes, hypertension, coronary heart disease, stroke and other cardiovascular diseases, hyperlipidemia, osteoarthritis, several types of cancers, gall bladder disease, sleep apnea, depression, and low self-esteem) and mortality. It seems likely that preventing obesity, and/or losing weight, might prevent or reverse at least some of these morbidities. Weight is frequently (usually) regained promptly after it has been lost if the weight loss was induced by weight-control drugs and the drugs have been discontinued. Certain drugs might maintain weight loss successfully in some individuals if drug administration were continued for longer periods of time. Since it is possible that a new "set point" will be developed at a reduced body mass, drug administration might be required for only a limited time; however, it is probable that drug administration must be continued indefinitely in order to reap the health and other benefits of reduced body weight. FDA standards for weight-control drug approval anticipate the investigation of long-term safety and efficacy of weight-control drugs, leading to approval of drugs with indications for weight control using long-term or indefinite drug administration.

3. EARLY CLINICAL TRIALS

For new chemical entities, the earliest clinical trials for tolerance, and kinetics are usually performed in obese subjects who are otherwise free of disease. It is desirable to include minorities (blacks and hispanics in particular) and both males and females in the clinical studies, including the earliest studies of tolerance, pharmacokinetics, pharmacodynamics, mechanism of action, and dose determination. The mechanism of action of the drug should be established if possible.

4. DOSE RANGE FINDING

Because a drug for weight loss may be prescribed extensively for relatively healthy subjects, it is particularly important that the drug dose recommended not be excessive. Dose-finding should identify the lowest dose of the drug that safely achieves an optimal drug effect. Inclusion of at least 3 doses of drug in dose-finding efficacy studies will probably allow identification of a low dose that is inadequate, and also a dose that achieves the maximum benefit that cam be obtained without toxicity. Trials should usually be randomized, double-blind, and placebo controlled, with all subjects, both on drug and placebo, receiving similar instruction in diet, exercise, behavior modification and other life-style changes, such as use of tobacco and alcohol. This does not mean that all studies must be conducted in patients that are practicing these life-style changes, but that in all studies instructions on life style should be similar in drug and placebo groups. Generally, subjects should be moderately to markedly obese (BMI at least 30 is suggested; other obesity measures may be preferred) but subjects may be healthy otherwise. The population should include minorities and both sexes if the target population is, broadly, overweight Americans. It is likely that 3-6 month studies in about 200 subjects will be required to show preliminary efficacy of the drug, but actual number depends on the amount of difference observed between the efficacy of drug and of placebo.

5. TRIALS TO ESTABLISH EFFICACY

Trials to establish efficacy of a weight loss drug should be randomized, double-blind, and placebo-controlled, with all subjects, whether on drug or placebo, receiving similar instruction in diet, exercise, behavior modification and other life-style changes. For the long-term efficacy studies, it is preferable to instruct all subjects in the relevant life-style modifications.

5.1 Population

For most weight-control drug studies, subjects in long-term trials should be moderately to markedly obese with body mass index (BMI) at least 30 for otherwise healthy individuals, and BMI at least 27 for those with comorbid conditions (hypertension, hyperlipidemia, glucose intolerance, cardiovascular disease, sleep apnea, or other obesity-related conditions). However, BMI does not distinguish size that is due to bone and muscle from that due to fat, nor does it identify subjects with visceral obesity, a potent predictor of morbidity. It is often preferable to identify obesity by methods that measure body fat and its distribution.

Type of obesity (peripheral or central, as indicated by measures of central obesity, such as waist-hip ratio or sagital diameter), presence and severity of risk factors and related co-morbidities, severity of obesity, and duration or age at onset of obesity may be factors that should be selected, excluded or stratified.

Ideally, the population will include minorities and both sexes in numbers adequate to allow measurement of response separately in men and women, and in blacks, caucasians, and hispanics.

Methods used to recruit subjects for obesity drug trials should be noted. Race, socioeconomic status, and education should also be included in demographic data.

5.2 Procedures

Subject Selection. Subjects who meet the entry criteria with regard to obesity and risk factors may be entered into a program aimed at weight reduction, but without drug. Such a program might include calorie-restricted or controlled diet, behavior modification, and exercise. As a minimum, a modestly restricted diet and regular exercise should be actively encouraged. Placebo may be used during this period so that placebo responders are identified. Generally, this program should be continued for 6 weeks. Subjects should not be placed on drug as long as weight loss continues without drug, but may be randomized when weight has plateaued, as long as their weight remains above their goal for weight reduction (e.g. ideal body weight). Although subjects who are still losing or who reach ideal body weight on this program have no need for drug at that time, they may be kept on the weight program and randomized to placebo or study drug later if their success at weight loss evaporates.

It is possible that the principal benefit of drug over placebo will be in maintaining weight loss. In this case, the studies that are of sufficient duration to detect a difference between drug and placebo in long-term maintenance of a loss obtained with the drug of interest or with other modalities (very low calorie or formula diet, intensive diet and exercise, etc.) will be most useful for demonstrating efficacy and for dose determination.

Endpoint evaluation

Actual weight loss should be reported, and, also, it is helpful to express weight loss in relative terms such as per cent of body weight or percent of excess over ideal body weight or change in body mass index. Measurement of change in central obesity is also useful.

At least two weight-loss demonstrations are possible:
1) demonstration that the drug effect is significantly greater than the placebo effect and the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5%.
2) demonstration that the proportion of subjects who reach and maintain a loss of at least 5% of their initial body weight is significantly greater in subjects on drug than in those on placebo.

Changes in risk factors or in waist to hip circumference or sagital diameter may be appropriate endpoints depending on the population to be studied. Development of diabetes, osteoarthritis or other complication of obesity may be a suitable endpoint in certain cases.

Measurement of obesity-associated cardiovascular risk factors (lipids, blood pressure and glucose tolerance) during drug administration is encouraged, as they may have a place in determining the balance of benefit vs risk for the drug. If one or more of these factors deteriorates or is not improved, the risk associated with this deviation must be considered in making a benefit-to-risk decision for the drug.

It may be advantageous to determine effects of drug-induced weight loss on quality of life and related factors. Favorable changes in risk factors and quality of life may be mentioned in the package insert and might lead to an indication for risk-factor alteration. Treatment of hypertension or type 2 diabetes may be a suitable indication.

Weight loss achieved with calorie restriction alone is usually associated with loss of both fat and muscle tissue. Exercise has been reported to reduce or eliminate muscle loss. A carbohydrate-restricted regimen will usually result in loss of body water. For these reasons, it may be desirable, at the start of the trials, to establish that the subjects have excess body fat by one or more of the accepted measurements, such as skin fold thickness, body circumferences or sagital diameter, under-water weighing, bioelectric impedance, and DEXA. Follow-up measurements can then confirm that body fat is decreased commensurate with the weight loss and that weight loss is not associated with excessive loss of body water or muscle. It may be of some interest to detect any change in visceral obesity, or in the small dense LDL that might be present in patients with abdominal obesity.

5.3 Duration of Trials

The demonstration of efficacy for long-term drug use, will usually include demonstration that the effect on weight is maintained for at least 12 months, i.e., the above mentioned (See

5.2 Endpoint Evaluation) conditions for demonstrating efficacy continue to 12 months after the initiation of treatment. Weight loss maintenance might decrease over time in both drug and placebo groups, even resulting in reversal of efficacy. Unless significant weight loss is maintained for at least 12 months, benefits on health and quality of life may be lost. In order to obtain an adequate estimation of the safety of weight-control drugs for long-term administration, generally, about 1500 subjects are expected to complete 12 months with 200-500 of those subjects completing 24 months of study. Most often the double blind status of the study is maintained for at least 1 year, at which time, placebo patients may be switched to drug and followed on open label for another 12 months to a total of 24 months for weight and development of obesity-related morbidities. For those who have dropped out of the study it is usually possible to obtain at least telephone contact at 24 months for self-reported weight, and morbidities.

It is not intended that this Guidance apply to all possible weight-loss drug evaluations. Special circumstances will obtain if the population or endpoints are not those envisioned in the Guidance. For example, it may be desirable to study a non-obese population for prevention of weight-gain, such as during cigarette withdrawal. Such specific indications may be proposed, with the appropriate rationale, to the Division of Metabolic and Endocrine Drug Products in order to obtain input on the proposed drug program.

As new drug entities with new modes of action are developed, modifications of the Guidance may become necessary and will be considered