Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products

Guidance for Industry

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

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Contains Nonbinding Recommendations

Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations to industry about the use of placebos and blinding in randomized controlled clinical trials in development programs for drug or biological products[2] to treat hematologic malignancies and oncologic diseases. This guidance does not address the statistical analyses that can be considered when data are unblinded in these trials.

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.

II. BACKGROUND

Placebos, defined as inert substances with no pharmacologic activity, are commonly used in double-blind, randomized controlled clinical trials. Blinding investigators and patients in these trials to the treatment patients are receiving decreases the likelihood of biased observations of the effectiveness outcomes, may decrease differential patient drop out, and allows for unbiased observation of outcome measures, which are particularly important when the assessment includes subjective endpoints. For example, a placebo-controlled study design may be useful or preferred in maintenance therapy, in add-on trial designs, in trials of adjuvant therapies (for which standard

[1] This guidance has been prepared by the Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* or *drug products* include both human drugs and biological products and drug-led and biologic-led combination products regulated by CDER and CBER, unless otherwise specified. This guidance does not apply to medical devices or device-led combination products regulated by the Center for Devices and Radiological Health.

of care is surveillance), and for indications where no treatment is available (best supportive care can be added to both arms to ensure all available care is provided to patients). However, in development programs for malignant hematologic and oncologic disease, the use of a placebo in double-blind, randomized controlled clinical trials may present practical and ethical concerns.

In many cases, because of the toxicity profile of the active treatment, patients and investigators may infer which treatment patients are receiving, so using a placebo control may not blind the treatment. For patients with hematologic malignancies and oncologic diseases that have standard effective therapy available, using a placebo (not an active treatment) generally would not be considered ethical, so an active control trial should be conducted. One such active control superiority trial design option is to conduct an open-label trial with a physician's choice of one of a few standard therapies as the comparator. In open-label comparative trials for which investigator bias may be of concern, a blinded central independent review of scans may mitigate bias regarding endpoint assessment.[3] Another option has been to compare the investigational drug product with the placebo, with each added to the standard of care (an add-on trial).

Continued blinding of patients and investigators at the time of disease progression or occurrence of serious adverse events is usually not acceptable. In a blinded immunotherapy trial, for example, a patient who develops suspected drug-related serious adverse events on the control arm may receive unnecessary treatments (e.g., immunosuppressive drug products including a high dose of glucocorticoids, cyclophosphamide, interleukin-6 antagonist, or infliximab) for management of adverse events incorrectly attributed to the investigational drug product.

Maintaining the blind after disease progression could also affect the selection and timing of a patient's subsequent therapy, potentially preventing a patient who had been on a placebo arm from receiving an approved therapy or delaying or preventing the patient's entry into other clinical trials (for those trials of similar drug products that may have specific exclusion criteria based on prior treatment with an active drug or class of drugs). Unblinding in those cases would therefore allow informed decision-making about additional treatment options (see below).

III. CONSIDERATIONS FOR USING PLACEBOS AND BLINDING

Given that using a placebo in randomized controlled clinical trials of therapies to treat hematologic malignancy and oncologic disease for which there is known effective therapy is ethically unacceptable, sponsors should consider using a placebo-controlled design only in selected circumstances (e.g., when surveillance is standard of care) or with certain trial design features (e.g., when the trial uses an add-on design). When considering a placebo control, sponsors should take the following into account:

- Sponsors should provide the rationale for the trial design. Justification is particularly important in the setting of a sham surgical procedure, when invasive methods are required to administer a placebo (e.g., intrathecal administration, intratumoral

[3] See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

administration, repeated intravenous administration via an indwelling catheter), when primary adverse event prophylaxis is required (e.g., antihistamine, acetaminophen, and/or corticosteroids to prevent infusion reaction), when there is an available therapy, or when a placebo is given as monotherapy and not combined with an active drug or drugs.[4]

- FDA does not require patient-level maintenance of blinding at the time of disease recurrence or progression. Unless there are no available appropriate treatment alternatives, FDA recommends unblinding only the patient and the investigator at the time of documented disease recurrence or progression by an objective measurement or measurements to ensure optimal patient management. If sponsors intend to maintain patient-level blinding when disease recurs or progresses and there are existing available treatments, the informed consent document should acknowledge the risks of this approach, and the protocol should include justification for the potential added risk.

- As stated in the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012), FDA recommends unblinding the patient and the investigator when the patient has an adverse event suspected to be related to the investigational drug product and for which management of the adverse event with one or more drug products with substantial toxicity or invasive procedures is being considered. In such cases of unblinding, the patient can be removed from treatment based on benefit-risk analysis, but the patient data should not be removed from the trial. If sponsors intend to maintain patient-level blinding when a suspected drug-related serious adverse event occurs, the informed consent document should acknowledge the risks of this approach, and the protocol should include justification for the potential added risk.

- Sponsors should provide a detailed description in the protocol and in the statistical analysis plan of the proposal for blinding (including whether the physiological effects or adverse events associated with the investigational drug product would lead to some degree of unblinding) and planned unblinding (unblinding driven by potential need for medicines with substantial toxicity or invasive procedures for managing adverse events).

[4] See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) and https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.