Hematologic Malignancy and Oncologic Disease: Considerations for Use of Placebos and Blinding in Randomized Controlled Clinical Trials for Drug Product Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Julia Beaver at 240-402-0489 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-204-8010.

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)

August 2018
Clinical/Medical

Hematologic Malignancy and Oncologic Disease: Considerations for Use of Placebos and Blinding in Randomized Controlled Clinical Trials for Drug Product Development

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, rm. 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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)

August 2018
Clinical/Medical

TABLE OF CONTENTS

Hematologic Malignancy and Oncologic Disease: Considerations for Use of Placebos and Blinding in Randomized Controlled Clinical Trials for Drug Product Development Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to industry regarding the use of placebos and blinding in randomized controlled clinical trials in development programs for drug or biological products[2] for the treatment of hematologic malignancies and oncologic diseases.

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. Because investigators and patients in these trials do not know what treatment patients are receiving, this can decrease the likelihood of biased observations, decrease differential patient drop out, and allow for unbiased assessment of outcome measures, particularly when the assessment includes subjectivity, such as for quality of life measures. A placebo design may be useful or preferred in maintenance therapy, add-on trial designs, or in trials of adjuvant therapies (where standard of care is surveillance). However, the use of placebo in double-blind, randomized trials conducted in development programs for drug

[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 *drug products* include both human drugs and biological products regulated by CDER and CBER unless otherwise specified.

products for the treatment of malignant hematologic and oncologic disease sometimes presents both 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 and thus use of a placebo control may not in fact blind the treatment. For patients with hematologic malignancies and oncologic diseases that have standard effective therapy available, use of a placebo (not an active treatment) poses ethical issues. If possible, an active control is often preferred over placebo, and one option has been to conduct an open-label trial with a physician's choice of one of a few standard therapies as the comparator. Another option has been to compare the investigational drug product to 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 presents additional challenges. For example, in a blinded immunotherapy trial, a patient who develops 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 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 would allow informed decision-making with respect to additional treatment options (see below).

III. CONSIDERATIONS FOR USE OF PLACEBOS AND BLINDING

Given the challenges of using a placebo in randomized controlled clinical trials for therapies to treat hematologic malignancy and oncologic disease, FDA recommends that a sponsor use a placebo-controlled design only in selected circumstances (e.g., where surveillance is standard of care), or with certain trial design features (e.g. if the trial uses an add-on design, when the endpoint intended to support a labeling claim has a high degree of subjectivity, such as patient-reported outcomes). When considering a placebo control, a sponsor 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 or when invasive methods are required for administration of the placebo (e.g., intrathecal administration, repeated intravenous administration via an indwelling catheter).

- 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 a patient at the time of documented disease recurrence or progression to ensure optimal patient management.

- FDA recommends unblinding the patient and 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 should not be removed from the trial.

- The sponsor should provide a detailed description in the protocol and statistical analysis plan of the proposal for blinding (including whether the physiological effects or adverse events associated with the investigational drug product will prevent effective blinding) and unblinding (including information regarding situations in which unblinding should occur).

- If a sponsor intends to maintain the treatment blind when disease recurs or progresses or a suspected adverse event occurs, the informed consent document should specify the risks and potential disadvantages of this approach, and the protocol should include justification for the potential added risk.