4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2015-N-1306]

Dose Finding of Small Molecule Oncology Drugs; Public Workshop

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public workshop.

The Food and Drug Administration (FDA), in cosponsorship with the American Association for Cancer Research (AACR), is announcing a public workshop entitled "Dose Finding of Small Molecule Oncology Drugs." The purpose of this 2-day workshop is to provide an interdisciplinary forum to discuss the best practices of dose finding and dose selection for small molecule kinase inhibitors developed for oncology indications. The goal is to foster robust scientific discussion to promote a movement away from the conventional 3+3 dose escalation trial design and move toward innovative designs that can potentially incorporate key clinical, pharmacologic, and pharmacometric data and, when appropriate, nonclinical information to guide dose selection. Ideally, this workshop will propel a movement toward integrating dose finding into the entire life cycle of product development as opposed to confining it to the Phase 1, first-in-human trial based on short-term safety measures.

Date and Time: The public workshop will be held on May 18 and 19, 2015, from 8 a.m. to 5 p.m.

Location: The public workshop will be held at the Washington Court Hotel, 525 New Jersey Ave., NW., Washington, DC 20001, 202-628-2100.

Contact Persons: Rasika Kalamegham, American Association for Cancer Research, 1425 K St. NW., Washington, DC 20005, 267-765-1029, Rasika.Kalamegham@aacr.org; and Christine Lincoln, Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD, 20993-0002, Christine.Lincoln@fda.hhs.gov.

Registration: Registration is free and available on a first-come, first-served basis. You must register online by May 14, 2015, 5 p.m. Registration will be handled through AACR. Early registration is recommended because facilities are limited and, therefore, FDA may limit the number of participants from each organization. If time and space permits, onsite registration on the day of the public workshop will be provided beginning at 7 a.m.

If you need special accommodations due to a disability, please contact the Washington Court Hotel no later than May 14, 2015.

To register for the public workshop, visit https://www.surveymonkey.com/s/WTM2Z57. Please provide complete contact information for each attendee, including name, title, affiliation, email, and telephone number. Registrants will receive confirmation after they have been accepted. Registrants will be notified if they are on a waiting list.

Streaming Audiocast of the Public Workshop: This public workshop will also be available via audiocast. Persons interested in accessing the audiocast must register online at https://www.surveymonkey.com/s/WTM2Z57. FDA has verified the Web site addresses in this document, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register. Early registration is recommended because

audiocast connections are limited. Organizations are requested to register all participants but to listen using one connection per location. After registration, participants will be sent technical system requirements and connection access information after May 14, 2015.

Comments: FDA is holding this public workshop to provide an interdisciplinary forum to discuss the best practices of dose finding and dose selection for small molecule kinase inhibitors developed for oncology indications. To permit the widest possible opportunity to obtain public comment, FDA is soliciting either electronic or written comments on all aspects of the public workshop topics. The deadline for submitting comments related to this public workshop is June 18, 2015.

Regardless of attendance at the public workshop, you may submit either electronic comments regarding this document to http://www.regulations.gov or written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

Transcript: As soon as a transcript is available, it will be accessible at http://www.regulations.gov. It may be viewed at the Division of Dockets Management (see Comments). A transcript will also be available in either hardcopy or on CD-ROM, after submission of a Freedom of Information request. Written requests are to be sent to the Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857. A link to the transcript will also be available approximately 45 days after the public workshop at

http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/default.htm. Select this public workshop from the posted events list.

SUPPLEMENTARY INFORMATION:

I. Background

Since the approval of imatinib in 2001, FDA has approved 26 small molecule kinase inhibitors for the treatment of oncology indications. For the first several small molecule kinase inhibitors in development, it was common to see multiple dose-finding trials that evaluated multiple dose levels and dosing schedules. As additional small molecule kinase inhibitors entered clinical trials and the familiarity with this class of drugs increased, the number of dose-finding trials for each compound reduced in number. Although this may appear to be a product of increased efficiency in trial design and dose finding, proper doses or dose ranges appear to not have been identified for approved products, as evident by the high prevalence of dose reductions observed in registration trials and the high frequency of postmarketing requirements to study alternative doses. In some cases, critical cross-disciplinary information does not appear to be integrated into the dose-finding process. Given the recent history of approvals based on the results of early phase trials driven by extraordinary efficacy data, the incentive for conducting rigorous dose-finding trials may not be overtly apparent. However, the increasing need for the development of combination therapy due to resistance to monotherapy and poor tolerance of approved dosing regimens underscores the need for a more efficient process of dose selection in the early stages of study design.

II. Summary

FDA's Center for Drug Evaluation and Research and the AACR agree to cosponsor a workshop focusing on providing a forum for discussion of best practices on dose finding of small

molecule oncology drugs. The workshop will be held May 18 and 19, 2015, and is expected to include between 10 to 13 panelists and speakers (including a moderator) per each of the 4 sessions and will be open to the public.

III. Purpose

The purpose of this 2-day workshop is to provide an interdisciplinary forum to discuss the best practices of dose finding and dose selection for small molecule kinase inhibitors developed for oncology indications. The goal is to foster robust scientific discussion to promote a movement away from the conventional 3+3 dose escalation trial design and move toward adaptive designs that can potentially incorporate key clinical, pharmacologic, and pharmacometric data and, when appropriate, nonclinical information to guide dose selection. Ideally, this workshop will propel a movement toward integrating dose finding into the entire life cycle of product development as opposed to confining it to the Phase 1, first-in-human trial based on short-term safety measures.

IV. Goals and Scope

1. To identify key best practices in the nonclinical evaluation of a compound, including, but not limited to, selectivity, pharmacology, secondary pharmacology, and toxicology.
2. To assess whether nonclinical information can be incorporated into the statistical assumptions of an adaptive dose-finding trial.
3. To discuss the best practices of integrating human pharmacokinetic and pharmacometric data, including drug interaction, when appropriate, into dose-finding studies.
4. To assess how drug exposure can be integrated into the statistical assumptions of an adaptive dose-finding trial and to assess whether evolving exposure data can be adapted into an ongoing trial.

5. To discuss barriers in moving away from 3+3 designs toward adaptive designs and to encourage creative dose-finding trial designs that can replace the conventional 3+3 dose-finding study, where appropriate.
6. To shift from conducting a large single-arm drug trial with the maximum tolerated dose based on a 28-day window to identify tolerable, biologically effective doses for confirmatory trials through prudent search of doses based on safety, efficacy, and patient tolerability.
7. To discuss potential regulatory implications of dose-finding studies, including, but not limited to, product labeling of dose ranges, dose titration, and postmarketing studies.

Dated: May 6, 2015.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2015-11536 Filed: 5/12/2015 08:45 am; Publication Date: 5/13/2015]