

had already been found to be resistant to or intolerant to imatinib.

In the *Medical Review*, the FDA reviewer stated that the clinical trials “were uncontrolled single-arm studies, because there is no effective comparator drug, and because a placebo control is deemed to be unethical.” The reviewer explained that “a placebo control would be unethical, because “patients with advanced stages of CML . . . are known to not have spontaneous cytogenetic or hematologic responses and generally have short survival.”

In comments about single-arm clinical trials, Daugherty et al. (68) state that, “[i]n diseases where spontaneous remission . . . are not observed, single-arm trials may be useful. A response rate (tumor size reduction) is considered a direct effect of the treatment as it is not usually observed in the untreated natural history of the disease.”

d. Telbivudine for Hepatitis B Virus

The following discloses the Sponsor’s decision tree in deciding not to use a placebo arm, but instead to use an active-control arm. The following also reveals how the Sponsor chose among the candidate drugs for the active-control arm.

Although the statistical design of the clinical trial was that of a noninferiority trial, the Sponsor hoped to find that its drug was noninferior, and also superior, with respect to the active control drug. The information is from NDA 22011, from December 2013 of the FDA’s website.

Design of the control arm was raised in the *Medical Review of telbivudine*, a drug for hepatitis B virus. The FDA reviewer provided the following timeline:

- *Lamivudine* for hepatitis B virus was FDA-approved in 1998.
- The Sponsor’s meeting with FDA, conducted after the end of its phase II clinical trial, and before the phase III clinical trial on *telbivudine* for hepatitis B virus, was held on June 17, 2002.
- Another drug against hepatitis B virus (*adefovir*) was approved shortly after the end-of-phase II meeting, where this approval was granted on June 20, 2001.

The FDA reviewer stated that there were “difficulties associated with a placebo-control design” and that the Sponsor “agreed that an active-control design was acceptable.” (Details on these difficulties were not disclosed in the *Medical Review*.) The reviewer pointed out that the only available active control was lamivudine, because of the fact that at the time of the end-of-phase II meeting, adefovir was not yet FDA approved.

In short, the trial design that was decided upon was a noninferiority trial, where the Sponsor’s goal was to demonstrate that telbivudine was no worse than lamivudine by a prespecified noninferiority margin.

Evans (69) discloses two situations where use of a placebo may be unethical. The first is where a single-arm study is preferred over one with a placebo arm, and this is for clinical trials where, “spontaneous improvement in participants is not expected.” The second situation, is for a noninferiority trial, where “a placebo is unethical due to the availability of a proven effective therapy.”

Actually, placebos were, in fact, used in the clinical trial on telbivudine. Because the study drug arm received large pills (600 mg telbivudine) and the active control arm received small pills (100 mg), it was the case

⁶⁸Daugherty CK, et al. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. *J. Clin. Oncol.* 2008;26:1371–8.

⁶⁹Evans SR. Clinical trial structures. *J. Exp. Stroke Transl. Med.* 2010;3:8–18.