different from the study drug. The FDA reviewer wrote:

> A disproportionate rate of premature treatment discontinuation, driven by higher rates of adverse events, must be taken into consideration in the interpretation of both safety and efficacy outcomes in this study. More patients in both of the everolimus groups prematurely discontinued study treatment and were subsequently switched to alternate therapy than in the Myfortic group [control group], which may **bias the interpretation** of the study results.

VI. AMENDMENTS TO THE CLINICAL STUDY PROTOCOL

After the Clinical Study Protocol is submitted to the FDA, the Protocol may be changed in response to new needs that arise during the course of the clinical study, such as a needed change in the study design. The desired changes are submitted to the FDA by way of amendments.

These changes may require approval by an ethics committee, as well as by the FDA. Amendments to the Clinical Study Protocol find a basis in the Code of Federal Regulations (CFR), as shown by the following excerpt from the CFR (139):

> (b) *Changes in a protocol.* (1) A sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:
>
> (i) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.
>
> (ii) Any significant change in the design of a protocol (such as the addition or dropping of a control group).
>
> (iii) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

A selection of actual amendments is documented below. The amendments usually fall into the categories of changes in dose, changes in number of subjects, changes in inclusion criteria for subjects, and changes in tests. This list of amendments to the Clinical Study Protocol provides an idea of the purpose of these amendments, but also serves as a summary of various elements that are typically found in clinical trials:

- Increase the dose (140)
- Eliminate the lowest dose (141)
- Change in inclusion criteria (142,143)
- Double the frequency of dosing (144)

[139]21 CFR 312.30 (b) (version of April 1, 2010).

[140]Bander NH, Milowsky MI, Nanus DM, et al. Phase I trial of 177lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. J. Clin. Oncol. 2005;23:4591–601.

[141]Zimmerman TM, Harlin H, Odenike OM, et al. Dose-ranging pharmacodynamic study of tipifarnib (R115777) in patients with relapsed and refractory hematologic malignancies. J. Clin. Oncol. 2004;22:4816–22.

[142]Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. New Engl. J. Med. 2010;363:1510–20.

[143]Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. New Engl. J. Med. 2009;360:668–78.

[144]Raetz EA, Cairo MS, Borowitz MJ, et al. Chemoimmunotherapy reinduction with epratuzumab in children with acute lymphoblastic leukemia in marrow relapse: a Children's Oncology Group Pilot Study. J. Clin. Oncol. 2008;26:3756–62.