Draft FDA Questions for the Neurological Devices Advisory Panel
March 17, 2011
P100034
NovoTTF-100A System for Recurrent Glioblastoma Multiforme (GBM)
NovoCure

1. A higher incidence of central nervous system (43.1%) and neuropsychiatric (10.3%) adverse events was observed in the Novo-TTF treatment group compared to the best standard of care (BSC) active control group. Do you believe this higher incidence of adverse events for the Novo-TTF group raises concerns regarding a reasonable assurance of device safety for the proposed indication?

2. According to the applicant's definition for the PP population, subjects receiving less than a 4-week cycle of NovoTTF-100A treatment (n=23) were considered a major protocol deviation and were excluded from the PP analyses. However, 16 subjects who received as little as one day/dose of chemotherapy were included in the PP analyses. Do you believe that inclusion of subjects with as little as one day/dose of a chemotherapeutic regimen in the BSC group for the PP analyses is appropriate? If not, please discuss the minimum treatment criteria for inclusion in the BSC PP group.

3. The IDE protocol listed five chemotherapeutic agents for the BSC group and stated that this list was representative of agents and dosing regimens that would qualify as BSC therapy. During the study, 25 subjects in the BSC group received chemotherapeutic agents, including Avastin, which were not explicitly listed in the protocol. However, the applicant's Per Protocol (PP) analysis selectively includes 14 Avastin-treated subjects who had a median overall survival time of 5.4 months, but excludes 11 subjects who received other non-listed chemotherapeutic agents with a median survival time of 10.2 months. Do you agree that the selective inclusion of Avastin-treated subjects is appropriate for the PP analyses?

4. Please discuss each of the following considerations for the ITT study population as they relate to the demonstration of effectiveness for the Novo-TTF-100A System for the proposed indication:

    a. Failure to show a statistically significant difference in the primary effectiveness endpoint (i.e., overall survival)
    b. Observed results in both primary and secondary effectiveness endpoints are comparable between NovoTTF-100A and BSC groups
    c. Quality of life surveys favoring NovoTTF-100A
    d. Post-hoc change in statistical approach from superiority to non-inferiority
    e. Comparability of the historical controls to the current study population

5. The applicant proposes the Novo-TTF-100A System to be used as a monotherapy, after surgical and radiation options have been exhausted, in place of standard medical therapy (e.g., chemotherapy) for recurrent GBM. Do you believe that the safety and effectiveness data support this proposed indication for use as monotherapy?

6. **FDA's inclusion of a question on a Post-Approval study (PAS) should not be interpreted to mean that FDA has made a decision on the approvability of this PMA device. The presence of post-approval study plans or commitments does not in any way alter the requirements for pre-market approval. A recommendation from the Panel on whether the device is safe, effective and if it has an appropriate risk/benefit profile, must solely be based on the premarket data. The following is FDA's question regarding potential post-approval studies if the device is approved.**

   Based on the safety and effectiveness data presented in this PMA, please discuss if a PAS is warranted in the event that the application is approved.

   If yes, please comment whether:

   a. the proposed IDE study population (newly diagnosed GBM) is appropriate to address the PAS safety and effectiveness of NovoTTF-100A intended for use in a population with recurrent GBM;
   b. the proposed primary and secondary endpoints for the PAS are appropriate;
   c. there are specific adverse events that need to be studied post-market;
   d. the study should include specific subgroup analyses.

Voting Questions

7. Is there reasonable assurance that the NovoTTF-100A System is safe for use in patients who meet the criteria specified in the proposed indication?

8. Is there reasonable assurance that the NovoTTF-100A System is effective for use in patients who meet the criteria specified in the proposed indication?

9. Do the benefits of the NovoTTF-100A System for use in patients who meet the criteria specified in the proposed indication outweigh the risks of the NovoTTF-100A System for use in patients who meet the criteria specified in the proposed indication?