Panel Questions: P130003 EDAP Technomed, Inc.
Ablatherm® Integrated Imaging High Intensity
Focused Ultrasound (HIFU)
July 30, 2014

Discussion Questions

*Effectiveness:*

1. For the principal analysis of the intermediate-term clinical information, the sponsor compares the 2-year biochemical survival rate from the HIFU IDE Cohort to a performance goal (PG) derived from the cryotherapy literature. Interpretation of this analysis is challenging for multiple reasons, including lack of validation of this endpoint as a surrogate for survival, and questionable appropriateness of, and justification for, the selected PG.
   a. Does biochemical survival rate at 2 years using Phoenix criteria demonstrate efficacy for a non-radiation treatment of patients with low risk prostate cancer?
   b. Is it valid to use a PG to evaluate the effectiveness of a new therapy for low risk prostate cancer?
   c. Do you agree with the validity of the proposed post-hoc, literature-derived PG?
   d. Do the results presented in the sponsor’s analysis demonstrate device effectiveness?

2. For the principal analysis of the long-term clinical information, the sponsor compares the 8-year cumulative metastasis rate following Ablatherm HIFU (1.1%) to that of the low risk subset of patients in the radical prostatectomy (RP) arm of the PIVOT trial (1.4%). The PIVOT trial failed to establish the superiority of RP to observation in the intention to treat population including all risk strata, and exploratory subgroup analyses of low risk patients revealed no significant difference for either survival or metastasis rate.
   a. Considering the low incidence of events observed in the PIVOT trial, is metastasis rate at 8 years a clinically useful endpoint for assessing efficacy of therapies in patients with low risk prostate cancer?
   b. Is comparison of Ablatherm HIFU to RP supportive of effectiveness, given that RP was not found to be different from observation?
   c. Do the results presented in the sponsor’s analysis demonstrate device effectiveness?

3. In the IDE study, where the protocol specified repeat prostate biopsy at 2 years post-HIFU, 28% of patients were documented to have a positive biopsy. Does this result support the effectiveness of this therapy?
Safety:

4. Prospectively collected safety data were obtained from the HIFU IDE Cohort (n=135) and the HIFU Prospective Safety Cohort (n=62). Additionally, safety data were obtained from a meta-analysis of the published Ablatherm HIFU literature. These sources of safety data demonstrate clinically significant morbidity with this non-surgical procedure. Common categories of adverse events included erectile dysfunction, urinary incontinence, urinary retention/obstruction, and stricture.
   a. Has the sponsor adequately characterized the safety profile of this device for its intended use?
   b. Which study cohort(s) would you use to characterize the safety profile?
   c. Please discuss whether the reported results demonstrate device safety for the intended population.

Post-Approval Study:

If the device is approved, the applicant is proposing to conduct a post-approval study (PAS) in which a cohort of subjects treated with whole gland Ablatherm HIFU in the U.S. will be followed for 8 years to assess the long-term performance of the device. Please discuss the following:

5. The primary effectiveness endpoint is the metastasis-free survival rate. Given the study population with low risk, localized prostate cancer, this endpoint may not be appropriate to evaluate long-term performance because of the extremely low rate that is expected. Please discuss the appropriateness of metastasis-free survival as the primary endpoint, and recommend any other effectiveness endpoints that should be included as primary or secondary.

6. Safety issues will be measured as secondary endpoints including morbidity at 2 years, and device and procedure-related adverse events. Please discuss if there are specific primary or secondary safety endpoints to be evaluated.

7. There is no comparator group in the applicant’s PAS proposal. Please discuss if a comparator group is needed, and if so, please provide recommendations on the appropriate comparator for the low risk prostate cancer patient population.

8. Please discuss if there are any other concerns that need to be evaluated in the post-market setting.
Voting Questions:

*Following the panel discussion, CDRH will ask panel members to vote on the following three questions:*

The Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system is a computer controlled device intended to thermally ablate the prostate gland (whole gland treatment) in cases of localized prostate cancer using HIFU energy. Treatment is delivered from an endorectal probe under ultrasound visualization.

The sponsor has proposed the following Indications for Use:

The Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system is intended for the primary treatment of prostate cancer in subjects with low risk, localized prostate cancer.

The following questions relate to the approvability of the Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system. Please answer them based on your expertise, the information you reviewed in preparation for this meeting, and the information presented today:

- **Voting Question 1:** Is there reasonable assurance that the Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system is safe for the proposed indications for use (e.g., the device will not expose patients to an unreasonable or significant risk of illness or injury)?

- **Voting Question 2:** Is there reasonable assurance that the Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system is effective for the proposed indications for use?

- **Voting Question 3:** Do the benefits of the Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system for the proposed indications for use outweigh the risks of the Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system in patients who meet the criteria specified in the proposed indication?

Panel members will be asked to state how they answered each question and to explain their answers. If the panel member answered “no” to any question, he or she will be asked whether changes to labeling, restrictions on use, longer term follow-up, or other controls, would change his or her response.
If the evidence provided is insufficient to allow for any of the determinations, the panel member should state this as the reason for answering “no.” A description of any remedial studies or actions should be given.