Sixty-Eighth Meeting of the

Obstetrics and Gynecology Devices Panel

Thursday, June 3, 2004
Holiday Inn, Gaithersburg, Maryland

InSightec ExAblate® 2000 (P040003)

DRAFT Discussion Questions

Safety and Effectiveness

1. The primary effectiveness endpoint is the Symptom Severity Scale derived from the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL). Success was defined as a "…10 point improvement in the Symptom Severity Scale of the UFS-QOL instrument in at least 50% of ExAblate patients at 6-months." (Please see Tab 8a (protocol) and Tab 8d of panel package.) Is the 10 point improvement a clinically meaningful measure of success?

2. The Intent-to-Treat (ITT) success rate at 6 months was 70.9% as indicated in the table below. The ITT success rate at 12 months was 40.4%. The success rate dropped in part due to patient loss-to-follow-up between 6 and 12 months. By 12 months, approximately 20% of the ExAblate subjects had undergone alternative treatment for their fibroids.

Intent-to-Treat Success Rates	
6 months	77/109 (70.9%; 95% CI: 61.2 – 79.0)
12 months	44/109 (40.4%; 95% CI: 31.1-50.2)

Secondary endpoints included fibroid volume changes at 6 months (ITT). On average 24.9% of the volume of the selected fibroid was treated.

Fibroid parameters	**Mean (standard deviation)**	
	6-months, n=91	**12 months, n=47**
Baseline fibroid volume	347.7 cc (240.7)	354.0 cc (181.8)
Fibroid volume at 6/12 months	310.5 cc (257.3)	321.6 cc (220.6)
Mean change in fibroid volume	37.2 cc (106.5)	32.5 cc (168.9)
Average % fibroid shrinkage	14.0% (29.4)	9.4% (44.3)

Do the patient-reported outcome data from the QoL instrument at 6-months and 1-year, when coupled with clinical results on 14% volume reduction of the treated fibroids, support the effectiveness of the ExAblate® 2000 for the treatment of uterine fibroids?

3. Has the Sponsor demonstrated that MR thermal mapping provides adequate intraoperative feedback during the treatment regimen sufficient to ensure safe and reliable dosing to the intended fibroid tissue?

4. A number of Adverse Events specific to ultrasound treatment occurred during the clinical trial, including nerve injury/leg pain, bowel symptoms, bladder symptoms, and skin injury. Do the

results from the thermal modeling and our understanding of the underlying physics provide sufficient information to understand the etiology of the injuries that occurred in the study?

5. Adverse Events as described above and other potential risks related to the use of the device prompted the development of active mitigations as identified in the attached chart. Are these mitigations sufficient to ensure adequately safe use of the device? Given the effectiveness achieved, do the benefits outweigh the risks for this device?

6. Total abdominal hysterectomy (TAH) was selected as the "control group" in this study in order to allow for some comparison of rates of recovery and serious adverse events between ExAblate and what has historically been the standard of care for symptomatic uterine fibroids. However, the demographics of the study group versus the control group vary widely in many aspects including BMI, incidence of diabetes, and incidence of hypertension (Tab 6 of panel package). Are the results of this open-label, non-randomized study sufficient to demonstrate clinically meaningful comparisons regarding the safety of the ExAblate procedure compared to TAH?

<u>Labeling & Training</u>

7. Does the panel have any comments on the labeling provided by the sponsor? Does the Panel have specific recommendations related to the proposed (See Tab 10 of panel package):

    ✍✍Indications (p. 332)
    ✍✍Contraindications
    ✍✍Warnings
    ✍✍Precautions
    ✍✍Adverse Events
    ✍✍Clinical Study

8. FDA and the sponsor agreed upon procedural requirements during the pivotal trial and in the continued access study to mitigate safety-related concerns (see attached table). Is the ExAblate® training system sufficient to ensure that the proposed mitigations are followed?

<u>Post-market Study</u>

9. Under current FDA guidance, patients from the pivotal study are scheduled to be followed for a total of 3 years after the procedure (1 year pre-market and 2 years post-market—protocol included in Tab 8b of the Panel package and titled "Long Term Follow-up Protocol-UF009"). Is there a need for additional post-approval studies or other post-market measures? If so, what is the purpose of such studies and what are the key elements of the study design?

    Note: Post-approval studies may provide additional information about an approved device; however, the safety and effectiveness must be demonstrated before approval. The results of a post-approval study should not be expected to change the "approval" status of the device.

Attachment to Ob/Gyn Devices Panel Discussion Questions

Risk	***Mitigation*** (pivotal study)	***Mitigation*** (continued access study)
Ablation of unintended tissue attributable to "enhanced volume effect"	✍ minimum 15 mm between focal volume and serosal surface or endometrium ✍ minimum 5 mm between focal volume and inner edge of fibroid capsule ✍ max "per fibroid" prescribed treatment volume limit of 33% ✍ Immediate post treatment MR contrast imaging used to confirm non-perfused volume for all patients as safety feedback on process.	✍ minimum 15 mm between focal volume and serosal surface (no endometrial requirement) ✍ focal volume within inner edge of fibroid capsule ✍ max "per fibroid" prescribed treatment volume limit of 50% ✍ immediate post treatment MR contrast imaging used to confirm non-perfused volume for all patients as safety feedback on process.
	✍ maximum 150 cc total fibroid volume ✍ maximum 100 cc per fibroid volume	✍ no change
Unintended heating of adjacent anatomy	✍ no focused energy through bladder ✍ MRI examination on day of treatment. ✍ minimum 90 sec 'cool down' between sonications ✍ the 15 mm from serosa ✍ Limit on total system power, and treatment plan limits, limit of 65-85C Tx temp.	✍ no change
Skin burns	✍ Improve acoustic coupling between skin and gel pad ✍ Shave patient pubic hair ✍ Skin prepped with alcohol to remove oil	✍ no change
Unintended heating of bone and nerve	none	✍ minimum 4 cm between treatment focus and any bone surface ✍ Angle between beam and sacrum ✍ Patient briefing