

# MR guided Focused Ultrasound for Uterine Fibroids

## Slide 1: Clinical Results: MR-Guided Focused Ultrasound for Uterine Fibroids

Hi, I am Ebby Stewart and the presentation today is on MR-Guided Focused Ultrasound for Uterine Fibroids. I am the Clinical Director for the Center for Uterine Fibroids at Brigham and Women's Hospital, and an Associate Professor of Ob/Gyn at Harvard Medical School.

## Slide 2: Feasibility FUS Study: Treating Women Before Hysterectomy

Our initial feasibility study employed women who were treated prior to planned hysterectomy. While this study was difficult to recruit for, it was important for a number of reasons. First we wanted objective assessment of treatment. At the time we were designing the study, Uterine Artery Embolization was being widely employed and yet it was not clear how the fibroids were undergoing necrosis was normal myometrium being necrosed, and we wanted to be able with this new modality of treatment to be able to ensure that we knew what was happening. We also designed the study so that we had close follow-up so that we did not miss any adverse events. We saw every woman within 72 hours so that we could detect problems early. Finally, we also felt that it was important to minimize risk to subjects by first treating women who had no desire to keep their uterus. Many of the women that we saw in this study felt that they had no options other than hysterectomy, but given the prevalence of fibroids in their family that this would be a study that would benefit their daughters and their granddaughters. By having tissue specimens that we could analyze and look at growth factor expression, we had a much better basis for understanding the biology of the process.

## Slide 3: MRgFUS Subjects Were Typical Fibroid Patients

The subjects seen in this initial feasibility trial were typical fibroid patients. We enrolled 55 women across several sites. They were in their late 40s, and their average BMI was 26. We did have women with BMIs as low as 19, or as high as 41. Certainly women who weigh over 250 pounds cannot be treated because they cannot fit into the MRI machine, but a huge number of women can be treated with this technology.

## Slide 4: MRgFUS Treatment Time Similar to OR Time

During the feasibility trial the median treatment time was approximately 105 minutes. And the time in the scanner, which involves both set up and confirmation of therapy was close to an hour longer. These treatment times have continued to be relevant, as we have continued to treat. However, with increasing experience a greater volume of tissue can usually be treated.

## Slide 5: MRgFUS: Most Subjects Able to Be Treated

We found that most subjects could be treated. This was a study without any lead ins. Seventy six percent of women had an adequate treatment. Of those who did not, approximately 5% had no sonications at all, and in half the cases, bowel was in the way of the treatment and was stopped

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for safety reasons. In the other half there were equipment issues that did not allow treatment. Of the remaining patients who had a suboptimal treatment, for most women this involved not being able to view the test sonication period. This is an important safety feature of the equipment that allows us to send a low energy pulse to confirm targeting before going to high-energy sonications. When the test sonication could not be visualized, treatment was stopped. This has become a very rare occurrence with future treatments with software modifications.

### **Slide 6: MRgFUS: Short Post-Op Recovery**

In the feasibility study we saw women within 72 hours in contrast to a procedure like Uterine Artery Embolization. Very few women were taking pain medication. Only 10% were taking any pain medication, and this included over-the-counter pain medication. We had an extensive list of questions we asked patients, and only approximately 25% had general discomfort; only 15% were complaining of pain or abdominal tenderness, and 10% of women had nausea at this time.

### **Slide 7: MRgFUS: Treatment Volume Small in Initial Study**

A limitation of the feasibility study is that a small volume was treated during these initial treatments. This is an initial study and the increase in volume has progressed with the increasing experience of operators.

By examining the hysterectomy specimens we were able to look at an important issue in the early clinical trial. We found that the area that appeared non-perfused on imaging following the procedure was approximately three-fold greater than the treatment volume. The question really was initially, is this an extension of treatment? If so, is it confined to the fibroid, or is there a danger that the thermal energy will spread? Or is it really an over estimate and represents potentially a stunned fibroid that is not killed by the process?

### **Slide 8: Extension of Treatment Area Detected by Imaging**

By examining the hysterectomy specimens we were able to look at an important issue in the early clinical trial. We found that the area that appeared non-perfused on imaging following the procedure was approximately three-fold greater than the treatment volume. The question really was initially, is this an extension of treatment? If so, is it confined to the fibroid, or is there a danger that the thermal energy will spread? Or is it really an over estimate and represents potentially a stunned fibroid that is not killed by the process?

### **Slide 9: Extension of Treatment Effect Confirmed at Hysterectomy**

This can be exploited therapeutically however, because with some extension you do not need to go to the furthest areas of the serosal surface to be able to get a complete treatment based on our current understanding.

### **Slide 10: Pain: Not What You See With UAE**

The thing that was most impressive to me in the initial clinical trial is the difference in pain that women experienced with focused ultrasound, compared to what was seen at Uterine Artery Embolization. I went into the clinical trial expecting to admit most women following the procedure, and to be able to continue to provide them with narcotic pain medication. What we found instead is something significantly different. During the treatment the pain levels got only to a level of mild on a scale of 0 to 3, approximately a 1.1 on average and that at the immediate evaluation in the

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recovery room after the procedure, the pain was not statistically different than pre-treatment. Discomfort was only mildly elevated. This is a very different patient experience than what occurs with Uterine Artery Embolization.

### **Slide 11: Adverse Events: Excellent Safety Profile**

We also had relatively minor adverse events and this is an excellent safety profile for a new device. There were approximately 4% of women having minor skin burns and 4% of women having increased bleeding following focused ultrasound. Given the nature of uterine fibroids and menorrhagia it is not clear whether these are procedure related. We only had one person who was hospitalized following the procedure for nausea following a late afternoon treatment, and there was one incidence of non-targeted sonication. In this case the sonication extended to the uterine serosa. There was no clinical sequella and the woman had a hysterectomy and damage was not seen to the serosa until evaluation of the pathology specimen. In retrospect this was due to incorrect targeting because of bladder filling, as we will discuss in a minute.

### **Slide 12: Lessons Learned: Feasibility Study**

So, in summary the lessons that we learned from the feasibility study are, first of all, to drain the bladder to keep the target from moving. The targeting of the uterine serosa in error occurred because the bladder filled and the target moved. Although we wanted to be as minimally invasive as possible to minimize problems during treatment, we chose in following procedures to keep the bladder drained by a foley catheter.

We also found that shaving the top part of the pubic hair mitigated against skin burns. Once shaving was implemented the number and the severity of skin burns decreased. Also, we should have intuitively known that going through an abdominal scar is very similar to targeting a uterine fibroid. The extra cellular matrix in both of these tissues tends to absorb energy, and the treatments are more successful and less painful to patients if the scars are included in treatment planning. There is an extension of therapy that suggests that a safety margin can be maintained.

### **Slide 13: Pivotal Study Design**

With the feasibility lessons in mind we went on to design the Pivotal study. These targeted 109 women treated with focused ultrasound and contemporaneously selected women at different sites undergoing total abdominal hysterectomy for comparison of adverse events. The primary outcome measure was the uterine fibroid symptomatology quality of life questionnaire, the UFS: QOL, which has been widely used for a number of fibroid studies, and together discusses symptoms related to the bulk of the uterus as well as bleeding. The initial study was designed as a six-month trial, and after some women had completed the protocol, an extension took place that followed all women to 12 months. These women are now all undergoing follow-up for three years.

### **Slide 14: Primary Efficacy End Point: Six-Month Symptom Severity Score Demonstrates Improvement**

This pie chart shows the % of patients that reached the 10 point improvement threshold for the Symptom Severity Score by Month 6 versus Baseline. The primary endpoint of the study was the Symptom Severity Subscale of the UFS: QOL. With this treatment protocol and intention to treat analysis showed that over 70% of women had a 10-point improvement.

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## **Slide 15: Symptom Severity Change: Baseline to 6 Months**

Not only did a large number of women have improvement, but the magnitude of improvement was substantial. If you look at the distribution of improvement, the threshold level to achieve success in this protocol was 10 points; however the average patient had almost 30 points of improvement. There were women in the protocol that had over 60 points of improvement on a 100-point scale. There were only seven women out of the protocol that did worse following focused ultrasound and one woman who was unchanged. The number of women who had improvement, but less than 10 points of improvement, was considered treatment failures for this protocol.

## **Slide 16:**

### **UFS-QOL: Symptom Severity Benefits Appeared Early Patients Continued to Improve**

The greatest magnitude of improvement appears to occur in the first three months following treatment. There is some continued improvement that is manifest from three to six months; however, generally there is a fairly prompt appearance of symptom reduction.

## **Slide 17: Disability Days**

There is a significant difference in terms of disability between hysterectomy patients and focused ultrasound patients. We asked a number of questions including things such as, “during the past four weeks how many days were you kept from usual activities, due to either uterine fibroid symptoms or your procedure”? You can see that at one month women undergoing hysterectomy have significant disabilities, whereas women already have a decrease in their disability from pre-treatment following focused ultrasound, and this continues up to three months. There were many women that felt that they could go back to work within a very rapid time, and in fact, the mean time to feeling normal was approximately 1.8 days.

## **Slide 18: Excellent Safety Profile**

The profile with focused ultrasound showed an excellence in safety. There were no deaths, no emergent surgical procedures, nor life-threatening events. There were also no hospitalizations for pain control and no circumstances of post-embolization syndrome. The most serious event that occurred during the trial was one patient who had a sacral neuropathy that was transient, and that had resolved by 12 months. In retrospect, the treatment planning has been used to mitigate this risk so that the far field energy is monitored. Once this mitigation step was taken there has not been recurrence of sacral neuropathy.

## **Slide 19: Pivotal Study: Limitations to Long-Term Efficacy**

One of the issues of using the Pivotal study to look at long-term efficacy is that there were substantial constraints placed on treatment. This makes sense given that this is the first indication for this new technology and maximizing safety is more important at an early stage than maximizing efficacy. The mean uterine volume was substantial in this study and the FDA protocol limited treatment to a 150 cubic centimeters per uterus. In essence, for most treatments an average of only 10% of the uterine volume was treated. Also, no cases were excluded at each center as a learning curve as is common in many devised trials.

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### **Slide 20: Continued Access Treatments Suggest More Complete Treatments Lead to Lower Symptom Severity Scores**

We have continued to treat women as time has gone on. The Pivotal study data is shown in red in this bar, and then the follow-up continued access protocol with very similar treatment parameters is shown in blue. However, as the procedure became FDA approved and treatment parameters were limited, more volume was able to be treated at a single setting. What we see is that it appears there is a more substantial decrease in the symptom severity score that we believe will transmit into long-term symptom recovery.

You can also see from this graph that even under the limited treatment protocols, there has been sustained symptom relief over 24 months.

### **Slide 21: Continued Access Treatments Suggest More Complete Treatments Lead to Increased Symptom Relief**

We are now also accumulating data that tells us that the greater the non-perfused volume achieved by treatment, the greater the decrease in symptom severity. What you see in this graph are the three time protocols: the Pivotal, the early continued access for protocol was similar and then the continued access protocol that allowed additional treatment. What we find is that if we can achieve a non-perfused volume greater than 30%, that we have increased improvement as monitored by the symptom severity score. It appears that this is likely very similar to what is seen with Uterine Artery Embolization. If you were able to get complete necrosis of the fibroid, you are more likely to have sustained symptom relief.

### **Slide 22: FDA Labeling for ExAblate® 2000**

The current labeling for the focused ultrasound device is that it is indicated for the treatment of premenopausal women who have symptomatic uterine fibroids and no desire for future fertility.

There are beginning to be anecdotal case reports of women pursuing pregnancy following focused ultrasound, and to-date, no pregnancy complications have been recorded.

Thank you for the opportunity to share this data with you.

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