

1 Dr. Stewart described the IDE pivotal
2 study of ExAblate, and I'm not going to repeat what
3 she said, nor will I repeat the primary and secondary
4 hypotheses, with the exception that I want to note
5 that the secondary hypothesis here, which was in
6 valuation of the trajectory of recovery in the two
7 treatment groups. The sponsor has already described
8 this. I am not going to talk about that any further.

9 Now FDA worked with the sponsor on the
10 pivotal study design, and we really perseverated on
11 what we consider to be potential for adverse events
12 with this device. We were nervous about the potential
13 for tissue necrosis of non-targeted tissue; in
14 particular beyond the uterus of the necrosis of tissue
15 up adjacent to the uterus, so we worked with the
16 sponsor to establish a very conservative treatment
17 planning program. And the list of items that
18 contributed to this was already discussed by Dr.
19 Stewart. But, for example, we felt that because this
20 is a very new type of technology combining MRI
21 thermography and focused ultrasound, and because we
22 have seen this volume effect that was greater than the

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1 targeted volume, we felt that it would be prudent to
2 begin here with limiting the volume of tissue that
3 could be targeted both within individual fibroids and
4 within the entire uterus.

5 I also want to add an important point
6 here. Our concern at the time that we were reviewing
7 this IDE for the pivotal study was in what I would
8 call near-term thermal damage. We were not, at the
9 time, sensitive to the fact, or that we might get
10 treatment effects in the far field. That is beyond
11 the area of focus, so that's going to be important
12 later in my talk, and critical when you hear from Dr.
13 Del Mundo later this morning; that we did not
14 appreciate the potential for effect in the far field.

15 Very generally, I'd like to just reiterate
16 a little bit about the baseline demographics between
17 the two populations. There was no difference in age,
18 essentially. The body mass index was higher in the
19 hysterectomy group. There was a significant
20 difference with respect to race, and with respect to
21 other chronic disease, there were some differences
22 between the ExAblate arm and the control arm. And

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1 specifically, women in the control arm had
2 significantly greater prevalence of diabetes mellitus,
3 hypertension, and anemia.

4 I just want to make a couple of simple
5 points with respect to this slide. First is that
6 you've heard about the symptom severity score of the
7 uterine fibroid symptom quality of life questionnaire.
8 It was the subset of that questionnaire, the symptom
9 severity score that formed the basis for the primary
10 endpoint in the study and the definition of success of
11 the study.

12 There were, however, two scores that were
13 taken prior to treatment. There was a screening score
14 to determine whether or not a patient was eligible for
15 the study. And then there was a score that's called
16 the baseline score. That's in maroon color on this
17 slide. And that baseline score formed the comparison
18 for the six-month evaluation, so the screening score
19 was only relevant to get into the study. After that,
20 it was the baseline score that was relevant to the
21 study success. But we thought that it would be
22 interesting for you to see that even before treatment,

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1 there were subtle differences in the scores that were
2 derived from that questionnaire.

3 And what this slide simply shows is the
4 distribution. Right in the very middle of the X axis
5 you see the word "unchanged", and right above that
6 "zero." And what this means is the 23 subjects had no
7 change in score between that screening questionnaire
8 and the baseline questionnaire. Beyond that, there is
9 a very roughly equivalent distribution on either side
10 of zero, but nevertheless, you can get the feeling for
11 actual numbers of subjects whose scores changed by a
12 particular range of points prior to treatment. Again,
13 this is all prior to treatment. And we think that
14 this will give you a feel for the stability of the
15 scoring instrument.

16 Okay. Now I would like to change gears a
17 little bit and talk about study success. And I just
18 want to mention that there are two ways to look at
19 study success. Intent to treat has a very strict
20 definition. Essentially, it is all patients enrolled
21 and treated, and all of these patients must be
22 represented in calculating the percentage success.

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1 Evaluable is a different way of looking at
2 it. The rules for an evaluable analysis are not,
3 frankly, as tight as they are for intent to treat, but
4 what evaluable permits one to do is to not be
5 penalized by counting subjects as failures who one can
6 argue really shouldn't strictly be viewed as failures.
7 But, nevertheless, from the most strict definition
8 standpoint, intent to treat, the percent success was
9 70.6. Remember that the primary hypothesis was that
10 greater than 50 percent would improve by a score of 10
11 points or better at six months. And the 70.6 is well
12 within the 95 percent confidence interval. It's well
13 above 50 percent.

14 And this slide again indicates that for
15 those subjects who achieved success, you can get a
16 feeling for how many of them met that primary endpoint
17 and by how many points. And what this also shows you
18 is that there were some subjects whose scores were
19 considered unchanged, and then some whose scores were
20 considered worse. And just because often we are
21 interested in well, what happened with those failures,
22 I'm just going to try to give you a quick rundown for

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1 the population at six months for whose scores worsened
2 and whose were unchanged.

3 Among patients who were considered to have
4 worsened scores were two treatment failures. These
5 subjects underwent hysterectomy. Two patients
6 withdrew, and subsequently one had hysterectomy. One
7 withdrew. She had an aborted treatment, but
8 nevertheless, she had a worsened score. One subject
9 was lost to follow-up, and had no six month quality of
10 life data. Seven women in this category completed
11 treatment, and they had actual worse scores following
12 treatment at six months.

13 Unchanged is a little bit different the
14 way we look at that. We asked the sponsor to consider
15 seven patients to have had zero change who were
16 treated with protocol deviations, because we felt that
17 the success rate for -- we feel that the success rate
18 for any study ought to reflect patients who are
19 treated according to the strict rules so that we can
20 write meaningful labeling, so the clinicians can
21 understand what they might expect. And that it would
22 be inappropriate to have the results reflect women who

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1 were treated outside the bounds of that treatment
2 protocol, so that explains seven of the subjects with
3 unchanged scores. Two had no six-month data, and one
4 actually had no score change.

5 And I should have mentioned, we have a
6 patient tree in your day-of folders, and it might help
7 you if you're interested in looking at those numbers
8 more closely in understanding what patients from the
9 original intent-to-treat populations fell into which
10 categories.

11 Now I'd like to just talk about patient
12 satisfaction. You've heard from the sponsor about
13 overall grouping of patient satisfaction and the
14 ExAblate group in general had high levels of
15 satisfaction. What I wanted to do here was just give
16 you a slightly different perspective, and in the
17 interest of doing that, here you can see satisfied
18 being broken down into three different categories,
19 very moderately in some. And similarly, patients who
20 describe themselves as dissatisfied, what level of
21 dissatisfaction did they experience. And for very
22 satisfied, the point here is that the hysterectomy

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1 subjects at six months were significantly more apt to
2 say they were very satisfied, compared to the ExAblate
3 group, which is probably not surprising because the
4 hysterectomy subjects did receive definitive treatment
5 for their fibroids. But nevertheless, we think that
6 it's important to keep perspective when you're
7 thinking in terms of patient satisfaction. There are
8 degrees of satisfaction, and they did differ between
9 the two groups.

10 Now at 12 months, you've heard that both
11 the intent-to-treat and the evaluable success rates
12 dropped. I should preface this by mentioning that
13 when the study was designed, FDA had a different
14 understanding regarding the length of follow-up than
15 the sponsor had. And it was a misunderstanding. We
16 expected three years of follow-up. The sponsor
17 believed that they were expected to follow the
18 patients through six months, so in all honesty, we
19 informed them very late in the pivotal study that they
20 would be required to follow-up these patients for up
21 to three years. And it created some difficulty for
22 them in terms of tracking down patients, and asking

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1 patients if they would continue to participate in the
2 study, so I think it's only fair to mention that. And
3 that helps to put some perspective on the next slide
4 where I talk about some of the women who were not
5 successes at 12 months, in part from an intent-to-
6 treat analysis. If they declined to participate,
7 they're considered failures; withdraw or lost to
8 follow-up, non-evaluables.

9 Significantly, though, we think it's
10 important to note that 23 women did have alternative
11 treatment as of 12 months, and many of these women had
12 hysterectomy by 12 months. Four of them had a second
13 ExAblate treatment.

14 You've already seen Dr. Stewart's slide
15 that covers this material. There are a couple of
16 things that I just want to highlight. One is that the
17 percentage of non-perfused volume of 23.6, that was
18 the average percent of non-perfused volume that is
19 immediately following the treatment. And then at six
20 months, the volume of the treated fibroids was
21 measured, and the percent shrinkage of the treated
22 fibroids was 15.3 percent.

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1 In looking at these numbers and thinking
2 about them, it's worthwhile again to think about the
3 fact that the treatment guidelines for the ExAblate
4 procedure only permitted the sponsor to treat up to 33
5 percent of any individual fibroid, and only up to 100
6 Ccs in any one fibroid up to 150 Ccs for an entire
7 uterus, so I think that part of what we're seeing
8 there reflects the conditions of the treatment.

9 You all have in your folder a list of
10 discussion questions that you'll be talking about
11 after lunch, and I want to bring to your attention
12 Discussion Question 1 now, because it relates to some
13 of the things I've been talking about. And it asks
14 you how you view the symptom severity scale of the
15 UFS-QOL as the instrument that was used to measure the
16 primary endpoint in the study, or that was used to
17 determine study success.

18 I'd also like to draw your attention now
19 to Discussion Question 2, just to kind of plant the
20 seed that this afternoon you're going to be talking
21 about essentially whether the study demonstrated the
22 effectiveness of the procedure. And in making that

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1 assessment during that discussion, FDA would request
2 the panel would consider the results from the symptom
3 severity score. And also, couple that with the
4 clinical results of actual volume reduction in making
5 your decisions.

6 I'm going to change speeds once again now,
7 and briefly talk about safety-related aspects of the
8 procedure. But I want to preface this by saying I am
9 going to ask you to focus at the end of my discussion
10 on two types of adverse events, and they were skin
11 burns and nerve injuries.

12 As Dr. Stewart described, we worked with
13 the sponsor prospectively before they started the
14 pivotal study to identify what we thought would be a
15 legitimate list of adverse events or complications
16 against which to compare the two study populations.
17 And the result of that comparison, not very
18 surprisingly, showed that there were relatively fewer
19 of the significant clinical complications in the
20 ExAblate group compared to abdominal hysterectomy
21 patients.

22 There were some other adverse events that

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1 are possibly more relevant to the ExAblate procedure,
2 and those are pain and discomfort, in particular,
3 during the procedure, menorrhagia post procedure,
4 urinary symptoms, nausea and vomiting. And then the
5 last two, skin burns and nerve injury that we do
6 believe are unique. We believe that these are unique
7 to this procedure, to ExAblate.

8 And I just want to conclude my discussion
9 of the safety evaluation in the pivotal study by
10 pointing out that in Discussion Question 6, you're
11 going to be looking at the relative safety of two
12 procedures, ExAblate compared to total abdominal
13 hysterectomy. We just want you to include in your
14 deliberation, or at least address the differences
15 between the study arm and the hysterectomy arm at
16 baseline, because there were some differences, and
17 provide your input to FDA with respect to how
18 comparable these two groups are, and what types of
19 conclusions we might be able to reach or not reach
20 regarding relative safety of ExAblate versus total
21 abdominal hysterectomy.

22 Now as you're aware, the sponsor has

1 permission to continue to treat patients with the
2 device, although the pivotal clinical study is over.
3 And of the aims of this, in addition to allowing
4 continued access, was to modify the treatment planning
5 in addition to improving long-term follow-up. But we
6 wanted to essentially liberalize the parameters for
7 treatment, and you can see that the sponsor is now
8 allowed to treat up to 50 percent of an individual
9 fibroid volume, as long as it's not a sub-serosal
10 fibroid. And the 15 millimeter margin, in retrospect,
11 didn't make much sense with respect to the
12 endometrium, so that has been eliminated. In
13 addition, the sponsor may perform one additional
14 treatment session. And as you see, increased maximum
15 duration of the treatment.

16 As of March, 89 patients had been treated.
17 The baseline demographics are similar to the pivotal
18 study, but there are three months safety data
19 available on only 53 to 54 subjects, so it is these
20 subjects who have been followed up for at least three
21 months who are going to be discussed by Dr. Del Mundo.
22 The preliminary efficacy data are good, 79 percent

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1 reported 10 point improvement in their symptom
2 severity score.

3 In the continued access study to-date,
4 there have been two instances of sonication-induced
5 leg pain, and the significance of these events,
6 whether or not they are nerve injuries, will be
7 described by Dr. Del Mundo.

8 In conclusion, I have attempted to give
9 you an overview of the effectiveness of the device as
10 seen in the pivotal clinical study, and to a limited
11 degree discuss the safety profile of ExAblate as FDA
12 understands it at this time. I have indicated to you
13 that two types of adverse events appear to be unique
14 to ExAblate, and that is skin burn and nerve injury.
15 And as you recall, there was a nerve injury even in
16 the feasibility population, but at the time, that was
17 a case of sciatica. At the time, we did not
18 appreciate how it might be related to this device.

19 Before Dr. Del Mundo presents a detailed
20 FDA analysis of those injuries, Loren Zaremba and
21 Bruce Herman are going to discuss for you the physics
22 of MRI thermography and focused ultrasound, and the

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1 results of some modeling, and how modeling can help us
2 understand the potential for heating of tissue in the
3 far field using ExAblate. Thank you very much.

4 DR. ZAREMBA: Good morning. My name is
5 Loren Zaremba. I'm an MR reviewer in the Radiology
6 Branch, Office of Device Evaluation. This morning I
7 will be discussing the role of thermal mapping in the
8 focused ultrasound of uterine fibroids using the
9 ExAblate 2000. I will discuss the advantages and
10 limitations of MR thermal mapping, and the safety and
11 reliability concerns with respect to the use of MR
12 thermal mapping for this intended use.

13 MR thermal mapping provides three major
14 functions in the ExAblate 2000. First, it allows
15 adjustment of the ultrasound focus location. This is
16 done by obtaining an image of the temperature
17 distribution produced by a low power sonication.
18 Second, it provides a measurement of the temperature
19 distribution during the treatment procedure. Third,
20 it provides feedback which enables the user to adjust
21 the power following a sonication if the temperature
22 was too high or too low.

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1 Temperature measurements are necessary
2 with any type of therapy which uses heating. Previous
3 devices, such as those approved for hypothermia have
4 used temperature probes. The ExAblate uses a new
5 approach, MR thermal mapping, which has the advantages
6 that it does not require surgical implantation. It
7 can be integrated with the MRI system, which is used
8 to visualize the uterine fibroids, and it provides a
9 temperature over the full MRI field of view, not just
10 a few points.

11 Also, unlike temperature probes, it does
12 not cause heating at the probe tissue interface which
13 can lead to an overestimate of the temperature with
14 those types of probes if they are not corrected.

15 The limitations of MR thermal mapping are,
16 first, it does not measure the actual temperature, but
17 change in temperature. Second, it cannot make
18 measurements in bone or fat. Third, a very small
19 amount of motion by the patient during the three
20 seconds required for MR thermal mapping can spoil the
21 measurement. Four, MRI thermal mapping has lower time
22 and spatial resolution than temperature probes. And

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1 five, calibration can present some difficulties.

2 I want to direct your attention to the
3 Discussion Question 3, has the sponsor demonstrated
4 the MR thermal mapping provides adequate
5 interoperative feedback during treatment regimen to
6 ensure safe and reliable dosing to the intended
7 fibroid?

8 With regard to safety, we have these
9 considerations; can temperature measurements be made
10 in all regions of interest? Are they sufficiently
11 accurate? Can they be made in time to allow
12 adjustments? And with respect to reliability, how
13 frequently does thermal mapping fail? If it fails, is
14 adequate backup provided?

15 With regard to the first safety factor,
16 the ability to measure temperature in all regions of
17 interest, the critical data showed that the ExAblate
18 is capable of measuring temperature in the principal
19 region of interest, the uterine fibroid, and in most
20 surrounding tissues. However, it cannot measure
21 temperature in the sacral nerves due to the fat
22 surrounding these nerves ,and also near the bone

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1 tissue interface where heating can be intensified due
2 to the very high ultrasound absorption by the bone.

3 In a later presentation, Dr. Del Mundo
4 will discuss the adverse events during the clinical
5 trial that may be related to nerve heating. Since MR
6 thermal mapping cannot provide the answer, we must
7 rely on thermal modeling to estimate nerve and bone
8 heating. The next speaker, Bruce Herman, will discuss
9 the modeling and results that have been done by FDA
10 with respect to nerve and bone heating.

11 Accuracy is relevant to the evaluation of
12 the ExAblate 2000 because if an incorrect reading of
13 temperature is given to the user, they could adjust
14 the power level higher, which could result in injury,
15 or lower, which could result in inadequate treatment.
16 MR thermal mapping measures the temperature change not
17 temperature. The ExAblate assumes that a sufficient
18 time has elapsed following a sonication that the
19 temperature has returned to a baseline of 37 degrees
20 Centigrade. The company recommends that the user wait
21 90 seconds before initiating the next sonication to
22 allow the temperature to return to baseline. However,

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1 this can be adjusted by the user.

2 If an adequate cool-down time is not
3 selected, the heating induced by the previous
4 sonication will add to that induced by the current
5 sonication, but this will not be shown by the thermal
6 map. This is of particular concern with regard to the
7 sacral nerves because modeling shows that the return
8 to baseline may take longer in the nerve region as
9 will be discussed in the next talk.

10 A second issue relating to accuracy is
11 temporal or time resolution. This is just the amount
12 of time it takes to make the measurement compared to
13 the heating period. The ExAblate requires a little
14 over 3 seconds to obtain a thermal map. The fibroid
15 can be heated very rapidly, and temperature can rise
16 10 degrees in the time needed to obtain a thermal map.
17 And the MR thermal mapping, the result is the average
18 temperature rise during measurement peak rather than
19 the peak. For all measurements but the final one
20 prior to the termination of the sonication, the
21 ExAblate assigns the temperature to the midpoint of
22 the measurement interval, which partially corrects for

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1 this. However, this is not done for the final
2 sonication.

3 The third issue relating to accuracy is
4 spatial resolution. In MRI, this is determined by
5 pixel size, which is about 1 millimeter by 2
6 millimeters for the normal ExAblate field of view.
7 Focused ultrasound produces very high temperature
8 gradients, which means the temperature falls off very
9 rapidly with distance from the focus. Thermal mapping
10 averages the temperature over a pixel, and that could
11 result in an under-estimate of the maximum temperature
12 for a small focal spot, or an under-estimate of the
13 size of the region ablated by sonication. However,
14 for the large group of spot sizes normally used in
15 treatment of uterine fibroids, this is not a serious
16 concern.

17 The last issue relating to accuracy is
18 calibration. In the case of MR thermal mapping,
19 calibration enables us to translate the observed
20 change in proton resonant frequency with temperature
21 into the temperature change. In the ExAblate, the
22 calibration factor relating the frequency change to

1 temperature change is assumed to 0.009 parts per
2 million per degree C, independent of the amount of
3 temperature rise, tissue type, or thermally induced
4 changes in tissue.

5 A calibration for MR thermal mapping
6 involves comparing the mapping results with an
7 independent temperature measurement method, such as a
8 thermal couple probe. Ideally, the calibration for
9 the MR thermal mapping used in the ExAblate should be
10 done for uterine fibroids in human subjects in order
11 to derive some indication of the variations between
12 fibroids, subjects, and other conditions of treatment.

13 We have an in vitro study using tissue
14 samples heated by a water bath, which indicates a
15 variation of 3 degrees. And we have an in vivo
16 calibration in rabbit muscle which indicates a
17 variation of 10 degrees.

18 One of the purposes of MR thermal mapping
19 is to provide feedback to allow adjustment of the
20 power following a sonication. However, there is a
21 delay in feedback from the thermal mapping. The
22 temperature versus time graph in the thermal ridges

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1 for a sonication are not displayed until the
2 sonication is complete. Consequently, a correction
3 cannot be made until the next sonication.

4 Among our reliability concerns is the fact
5 that a very small amount of patient motion can result
6 in a loss of a thermal map. The temperature
7 measurement cannot be repeated because this would mean
8 re-sonicating the same spot.

9 The failure rate for thermal mapping
10 appears to be quite low. InSightec estimates it is
11 only about 4 percent, and since the treatment consists
12 of a large number of sonications, this may not be a
13 concern. The user is instructed to check the fiducial
14 markers to determine if movement was sufficient to
15 affect the treatment.

16 Another reliability concern is the
17 availability of an alternate means of assessing its
18 effects over the treatment; i.e., a backup method. If
19 the thermal maps are lost, the so-called magnitude
20 images may not be adversely affected. Magnitude
21 images display signal strength and are not as
22 sensitive to motion as thermal images. However, the

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1 magnitude images may be of limited usefulness in
2 displaying the effects of the sonication on fibroid
3 tissue. The final confirmation of the effect of the
4 treatment is contrast enhanced image obtained after
5 the treatment.

6 In summary, MR thermal mapping provides
7 significant advantages over other available
8 technologies in that it is non-invasive, can be
9 integrated into MRI system use to visualize the
10 pathology, provides a thermal map over the full MRI
11 field of view, and does not interact with ultrasound.
12 The major limitation is that it cannot measure
13 temperature in bone or fat, which prevents estimation
14 of the heating of the bone and sacral nerves in the
15 far field. The limitations associated with
16 sensitivity to motion and lower temporal and spatial
17 resolution are not serious. And the calibration of
18 the method can probably be improved with additional
19 studies.

20 I would now like to turn the discussion
21 over to Bruce Herman, who will describe the thermal
22 modeling that has been done.

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1 MR. HERMAN: Hello. My name is Bruce
2 Herman. I'm a Physicist with the Office of Science
3 and Engineering Laboratories within CDRH. I'll be
4 discussing the thermal effects distal to the focus
5 using the ExAblate as regards possible adverse thermal
6 effects. My presentation will not be an exhaustive
7 discussion of every concept that might affect the
8 thermal modeling, but I hope to give a relevant
9 background and orientation.

10 I will be discussing the concept of
11 thermal dose, some factors affecting the temperature
12 rise of the sacral nerve, and the bone, and the so-
13 called far field of the ultrasound beam. I'll be
14 talking about the limitations of the knowledge
15 regarding tissue characteristics, which are relevant
16 to modeling the temperature rise in these structures.
17 I'll give a couple of temperature rise simulations,
18 and I'll talk about the limitations of these models.

19 As Dr. Zaremba mentioned, it's important
20 because magnetic resonance thermal imaging can not
21 determine the temperature rise near bone or in fat
22 which might typically surround nerves, which means

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1 that theory, i.e., modeling, plus, of course, clinical
2 trial results are very important to assess the safety.

3 In most biological systems for temperature
4 rises -- with temperatures above 43 degrees, which
5 corresponds to a 6 degree temperature rise assuming
6 the baseline temperature of 37 in the body, each
7 temperature rise of 1 degree C requires housing the
8 exposure time to achieve the same level of effect. If
9 the temperature is a varying function of time and T-43
10 is the time necessary to achieve an effect at 43
11 degrees CI, a 6 degree temperature rise, and the time
12 necessary to achieve an effect for a time varying
13 temperature is given by this integral equation. It's
14 not just the peak temperature that's relevant, but the
15 temperature and the time over which a particular organ
16 sees that temperature, which is relevant to assess the
17 propensity for any type of damage due to an organ or
18 structure.

19 This gives a report of thermal dose
20 thresholds for cell damage for certain tissue types.
21 We receive for muscle, fat, and fibroid, typically 42
22 degrees C. The time necessary to see an effect is

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1 14,400 seconds, which corresponds to 240 minutes. At
2 51 degrees C, though, the time required drops to 56
3 seconds, 53, 14, 55 degrees Celsius, to 3.5.

4 With more sensitive structures, such as
5 nerve, colon, or intestine, reported times for effects
6 at 42 degrees C have been between 1,500 and 3,600
7 seconds. This corresponds to a time of 10 seconds at
8 51, 2.4 seconds at 53, .6 at 55. Rule of thumb might
9 be for these more sensitive structures, as you get
10 into the lower 50s, you might begin to see some type
11 of damage.

12 Of course, for all these structures when
13 you get to be above 65 degrees C, the damage occurs
14 almost instantaneously, and you get pretty much
15 ablation almost instantaneously, as has been mentioned
16 in previous presentations.

17 This slides shows - and it's not drawn to
18 scale - shows the ultrasound transducer focusing the
19 beams with very high intensity within the region of
20 treatment within the fibroid. The beam distal to the
21 focus then spreads out, and the intensity is lowered
22 both due to the spreading-out of the beam, and due to

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1 absorption in the intervening layers.

2 In the far field of the beam, you might
3 have a structure such as sacral nerve surrounded by
4 fat, and it might be near a bone. You can think of
5 the absorption in let's say the sacral nerve as a
6 combination of two types of phenomena; one, direct
7 absorption in the nerve and in the fat surrounding the
8 nerve. And if it's near the bone, then since the bone
9 is such a highly absorbing material, as we'll see, it
10 then will conduct heat to the sacral nerve after
11 absorbing a lot of the ultrasound energy.

12 As the nerve gets closer to the bone, this
13 phenomena might become prominent, predominant. And
14 as, of course, it gets further away from the bone but
15 closer to the focus with higher intensities, the
16 direct absorption might be the predominant mechanism
17 of temperature rise.

18 The temperature is a function of, of
19 course, the local intensity, the absorption of
20 ultrasound by the structures, the incidence of the
21 ultrasound beam on the bone. I mention this because
22 if an ultrasound beam is normally incident on the

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1 bone, most of the energy is absorbed by the bone. But
2 if it's offset or comes at an angle greater than about
3 30 degrees to normal, most of the energy is actually
4 reflected and not absorbed, so the bone heating would
5 not be a strong factor.

6 Of course, the beam restructures size, as
7 we'll see is important. The thermal characteristics
8 of the tissue, such as thermal conductivity, heat
9 capacity are important, and the geometry, the size,
10 how close one structure is to another. I want to
11 emphasize, basically it's a complicated phenomena,
12 multi-parametric phenomenon.

13 This slide shows the range of reported
14 tissue absorption value. As you can see, for various
15 tissues, there's a wide range of reported values.
16 This is important because for a lot of structures, the
17 direct absorption, the temperature rise due to direct
18 absorption is approximately linear with the absorption
19 value, how much of this energy it absorbs.

20 Now these red diamonds are the values used
21 by InSightec in their modeling. Now they are commonly
22 accepted values for tissue absorption, do cluster

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1 around the red diamonds. But I wanted to emphasize
2 that these values, which will be used in modeling
3 you'll see, come with very large error bars.

4 We talked about that the size of a
5 structure might be critical in determining the
6 temperature rise. This shows, for one, soft tissue
7 absorption model, that for the stated incident
8 intensity, the temperature rise after 20 seconds is a
9 strong function of the dimensions of the structure,
10 for something on the order of 1 millimeter, .1
11 centimeters, the temperature rolls over very quickly.
12 And after 20 seconds, the rise is not very great.
13 Whereas, for a large structure, such as the .3
14 centimeter structure, the temperature stays linear up
15 to 20 seconds, and you get a much higher temperature
16 rise. We use 20 seconds because that is the
17 sonication time used by the ExAblate.

18 This is a simulation which was actually
19 done by InSightec which shows the temperature rise at
20 a sacral nerve 3 millimeters from the bone, and
21 surrounded on all sides by 3 millimeters of fat. It
22 utilizes a focus-to-bone distance of 40 millimeters,

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1 which again, InSightec showed a slide that showed this
2 is the current protocol for use, to keep the bone at
3 least 40 millimeters away from the focus, and it uses
4 a power of 250 acoustic watts. This is the maximum
5 power that this transducer can put out, so this is a
6 worst, worst case.

7 The red curve shows the temperature right
8 at the sacral nerve without the bone and so gives an
9 indication of the direct absorption, the temperature
10 rise due to direct absorption of energy, and the blue
11 line shows the temperature rise with both
12 contributions, the bone and the direct effect. As you
13 can see, the temperature rise for this case get into
14 the mid-50s or the low 50s. But again, I want to
15 mention that if we assume a higher absorption than was
16 used, this red curve could be quite a bit higher than
17 was assumed in this model.

18 This next, again an InSightec model, shows
19 the same situation, but here the protocol demanded
20 focused temperature is equal to 85 degrees. Again,
21 the protocols currently demand that the temperature at
22 the ablation focus should be no greater than 85

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1 degrees. And, of course, this would consequently
2 lower the total power needed. And this gives the
3 temperature rise again at that same sacral nerve with
4 and without bone.

5 As you see, the temperature rises are
6 lower. It goes from 37 to 41 without bone, and goes
7 to about 44 with. But again, I want to emphasize that
8 the if the absorption values used are higher, these
9 temperatures will go up. If the sacral nerve is
10 closer to the focus, let's say it may be 13
11 millimeters away instead of 3 millimeters away, this
12 bone contribution will be less, but the contribution
13 due to direct absorption could be as much as 75
14 percent higher. Again, emphasize the complexity of
15 the situation.

16 Actually, I do want to mention the fact
17 that we see that we have a 20 second sonication time
18 and then a 90 second cool down time. And this model
19 shows that even after the 90 second cool down time in
20 the far field, there's still a significant temperature
21 rise, which may mean that if there is any overlap of
22 two consecutive sonications on the bone or on the

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1 structure, you might get some addition of temperature
2 to the second sonication from the first.

3 This is a model done by CDRH. This shows
4 a temperature rise at the bone tissue interface again
5 for 85 degrees for the focus, and a focal bone
6 distance of 40 millimeters. It assumes no fat between
7 the focus and the bone, so the maximum energy hits the
8 bone. Again, this has arised at the bone tissue
9 interface. As you can see, we have two consecutive
10 pulses, 20 seconds on, 90 seconds cool down.
11 Temperature rises can be very high, so if by chance a
12 nerve structure is right at the bone, it can
13 experience quite high temperatures due to bone
14 heating. Again, a significant temperature rise after
15 the 90 seconds, so you might have a partial additive
16 effect if there's an overlap.

17 Again, I want to emphasize these last
18 three slides assume normal incidence of the ultrasound
19 beam on the bone, meaning maximal energy absorption by
20 the bone. The current protocols used by ExAblate try
21 to maximize the angle of the beam on the bone to avoid
22 this absorption by the bone. And, of course, these

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1 temperature rises would go down consequently if the
2 beam did come in at an angle of 30 degrees or more
3 from the normal.

4 Okay. The factors that may cause
5 temperature rises higher than those models by CDRH or
6 InSightec could be higher absorption values than
7 assumed, larger structures than assumed, structures
8 closer to bone or focus, possible inaccuracy of the
9 temperature map at the focus. If it reads low than a
10 higher intensity to cause 85 degrees to the focus
11 might be used and is necessary, which would increase
12 the intensity in the far field. Incorrect thermal
13 conductivity or heat capacity, and possible overlap of
14 consecutive sonications.

15 Now in conclusion, the modeling using
16 generally accepted values for tissues parameters,
17 together with the discussed protocol caveats, predict
18 reasonably that thermal events of adverse effects in
19 the far field should be very rare. But given the
20 range of imported and possible actual variability of
21 tissue values, the individual range of structure
22 geometries, the accuracy of MR, et cetera, this

1 modeling in and of itself does not allow adverse
2 thermal effects to be totally ruled out, which of
3 course means that clinical results take on added
4 importance in assessing the accuracy of the modeling
5 and the actual risk benefit. And I gather that the
6 clinical situation is consistent with these
7 conclusions.

8 As regards this, Dr. Del Mundo will
9 shortly present specific adverse effects that have
10 occurred during use of the ExAblate, and will discuss
11 how we and InSightec have used this modeling to try to
12 understand and prevent such events. Again, as regards
13 this also, you will be presented with a discussion
14 question for this afternoon. Basically the question
15 is, do the results from the thermal modeling and our
16 understanding of the underlying physics allow
17 sufficient information to understand the etiology of
18 the injuries that occurred in the study and, of
19 course, to mitigate their occurrence? Dr. Del Mundo
20 will now give his presentation.

21 DR. DEL MUNDO: Thank you, Bruce, and good
22 morning. I'm Noel Del Mundo, Medical Officer in the

1 OB-GYN Devices Branch. I will be presenting the
2 safety analysis of sonication-related adverse events
3 that occurred during the pivotal trial.

4 I will focus on the description of the
5 types and severity of skin burns and nerve injuries
6 that occurred during the pivotal trial. I will
7 provide the analysis of possible causes of the
8 sonication-related adverse events, and I will then go
9 through the list of possible mitigations to prevent
10 each type of adverse event, and I will provide the
11 preliminary safety results from the continued access
12 study in which the mitigations were implemented.

13 Of the adverse events that Dr. Corrado had
14 previously summarized for you, the most notable
15 sonication-related adverse events were skin burns and
16 nerve injuries. IN all, there were five first or
17 second degree skin burns during the pivotal trial.
18 Improper acoustic coupling between the skin and the
19 gel pad can result in undesired heating of the skin.
20 In other words, any areas between the skin and the
21 transducer that allows for increased reflection of the
22 ultrasound energy can cause heating of the skin and

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1 possible skin burn. Examples are air bubbles present
2 in the skin folds and around the hair, oil between the
3 skin and the transducer.

4 In all the cases of first and second
5 degree skin burns, all patients had hair in the
6 sonication pathway. And also, early in the pivotal
7 trial the patient moved and decoupled from the
8 acoustic gel, resulting in a first degree skin burn.

9 The steps in the training manual to reduce
10 the risk of skin burns want the patient to shave the
11 hair from the lower abdomen to two centimeters below
12 the pubic synthesis. The abdominal is cleaned with
13 alcohol to remove oil on the skin, and patient
14 movement is limited with a table strap. And lastly,
15 the MR planning images are examined for air bubbles at
16 the skin-gel interface and for skin folds.

17 These steps were re-emphasized to the
18 investigators during the pivotal trial and prior to
19 the continued access study. Preliminary results on 54
20 patients treated in the continued access study
21 suggests that the mitigations and retraining have
22 reduced the incidents of skin burns as no cases of

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1 skin burns have been reported.

2 I'd like now to focus on the nerve
3 injuries. These injuries have been the subject of
4 extensive review by FDA and InSightec. In all, there
5 were five cases of sonication-related nerve injuries
6 during the pivotal trial, and the patient's symptoms
7 lasted anywhere from two days to twelve months.

8 In addition to the five nerve injury
9 cases, there were three cases of what we're calling
10 nerve stimulation. These cases differ from the nerve
11 injury cases in that the leg pain did not extend
12 beyond the day of treatment, but we think that in the
13 continuum of unintended heating of the nerve by
14 unfocused ultrasound, these cases represent the mild
15 form of heating of the sacral and sciatic nerve in the
16 far field of treatment. This is a point that I'll get
17 back to in subsequent slides.

18 Now getting back to the five cases of
19 nerve injuries, InSightec analyzed these cases and
20 found that common to all five cases were the
21 following. Lower extremity pain was acutely felt by
22 the patient during the treatment. The distribution of

1 pain is consistent with either sacral or sciatic nerve
2 injury. There was rapid onset of pain during the last
3 three to five seconds of sonication, and the sacral
4 nerve or sciatic nerve bundle was identified in the
5 far field of the ultrasound beam.

6 There appears to be varying degrees of
7 peripheral nerve injuries related to sonication. A
8 mild effect is nerve stimulation resulting in leg pain
9 which resolves the day of treatment. The next degree
10 of effect is nerve injury resulting in the
11 interruption of nerve function without anatomic
12 discontinuity axon. This injury can take days to
13 weeks to recover.

14 The most severe form of sonication-related
15 nerve injury we have seen in the pivotal trial
16 resulted in the interruption of the axon, requiring
17 regrowth of the axon. This injury can take months to
18 recover and considered permanent if symptoms persist
19 for greater than two years.

20 This worst case was that of Patient 919,
21 which occurred near the end of the pivotal trial. The
22 patient complained of leg pain at the completion of

1 the sonication treatment, and developed left lower
2 extremity weakness. She had difficulty walking and
3 climbing stairs. She had numbness and tingling from
4 her left calf to the dorsum of her left foot.

5 She was evaluated by a neurologist at six
6 months, and physical examination revealed that nerve
7 injury consistent with neuropraxia had resolved.
8 However, minor deficits present at six months due to
9 axonal loss would recover over a much longer time
10 point as the axon has to regenerate from the pelvis
11 all the way to the target muscle.

12 Evaluation at 11 months by the same
13 neurologist showed that the patient had almost fully
14 recovered, except that she was unable to flex her left
15 toe. She had otherwise returned to her baseline level
16 of activity.

17 Now because of the symptomatology and
18 because of the location of the sacral nerve bundle in
19 the far field of the beam, it's believed that this
20 patient sustained injury to the sacral nerve bundle
21 located in close proximity to the sacrum. This axial
22 MR image of the pelvis is to show the proximity of the

1 anatomic structures of concern. This is not an image
2 taken from an actual treatment of Patient 919.

3 To orient the audience, the patient is
4 laying face down, and at the bottom of the screen is
5 the abdomen, and at the top of the screen is the
6 patient's back. The structures of particular interest
7 to us are the sacrum pointed to in a dark blue arrow,
8 and the sacral nerve, 4 centimeters away from the
9 treatment volume pointed to by the red arrow, and the
10 treatment volume represented by the rectangle, pointed
11 to by the orange arrow.

12 As was mentioned by Dr. Zaremba, since MR
13 thermography cannot provide temperature measurements
14 at the bone or at the interface between the nerve and
15 the bone, the company has provided temperature
16 modeling to help explain how nerve injury could have
17 occurred in Patient 919. This temperature graph is
18 slightly different format from that that was presented
19 earlier by Bruce Herman. This graph shows the
20 temperature as a function of distance from the
21 transducer. The temperature graph depicted assumes
22 that the angle of sonication is perpendicular to the

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1 sacrum, and the baseline temperature is at 37 degrees
2 Celsius.

3 When the focused ultrasound causes
4 temperature to rise to 85 degrees Celsius at the
5 treatment focus in the fibroid, unfocused energy in
6 the far field causes the temperature to rise at the
7 nerve to 42 degrees Celsius, and 55 degrees Celsius at
8 the sacrum.

9 Following the caveats previously mentioned
10 by Bruce Herman, if the peak temperature at the
11 treatment focus is higher than 85 degrees Celsius, the
12 temperature at the nerve and bone will be higher
13 proportionately. Conversely, if the incidence angle
14 is turned away from the perpendicular to the sacrum,
15 the amount of absorbed energy to the bone will be
16 less, decreasing the rise in temperature at the bone.
17 And also, the temperature at the nerve will increase
18 if the nerve is closer to the bone.

19 The previous graph had assumed that the
20 baseline temperature was at 37 degrees Celsius
21 throughout the beam path. Now this temperature
22 modeling is of the nerve tissue 4 centimeters from the

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1 treatment focus. The red line shows that if the nerve
2 is in close proximity to the bone, the temperature
3 will be at 39 degrees Celsius at 90 seconds after
4 completion of the treatment.

5 The blue line, on the other hand, shows
6 that if the bone is in close proximity to the nerve,
7 the temperature will be 42 degrees Celsius 90 seconds
8 after the completion of the treatment.

9 Now if the length of cooling time is not
10 extended beyond the nominal 90 seconds, the cumulative
11 effect of this small difference in temperature can be
12 significant after a series of sonications.

13 Bruce had previously shown this
14 temperature graph of the nerve in very close proximity
15 to the bone. It illustrates the concern for adequate
16 cooling time between sonications that I had mentioned
17 in the previous slide. From a practical clinical
18 standpoint, as the user becomes more efficient at
19 targeting and sonicating a focus in a fibroid, the
20 nominal 90 seconds of cooling time becomes
21 insufficient to allow the sacral and sciatic nerve to
22 return to baseline temperature before subsequent

1 treatment is initiated; thus, increasing the risk for
2 nerve heating and injury.

3 From the temperature modeling, the
4 possible steps to prevent heating of the sacral and
5 sciatic nerve are to alter the incidence angle of the
6 beam to decrease the amount of absorbed energy at the
7 bone, establish a minimum distance from the treatment
8 focus to the sacrum, lower the peak temperature at the
9 treatment focus, and possibly increase the cooling
10 time between sonications to allow the bone and nerve
11 temperature to return to baseline before subsequent
12 treatment.

13 Of these, the company has implemented in
14 the training module, a change in incidence angle away
15 from perpendicular when the sacrum is 4 centimeters
16 away from the treatment focus, and to maintain a
17 minimum distance of 4 centimeters when the sacrum is
18 in the far field of the beam.

19 Now working with the company, we recently
20 compiled the incidence angle and distance data to see
21 if the current mitigations if implemented in the
22 treatment of the five patients with the nerve injury

1 would have prevented the nerve injury. From this
2 chart we can see that the most severe case could have
3 been prevented, but clearly, two cases meet the
4 requirement greater than 4 centimeter distance, and
5 greater than 30 degrees change in the incidence angle.

6 The question is, are additional steps such
7 as lowering the peak temperature at the treatment
8 focus and increasing the cooling time warranted to
9 decrease the risk of nerve injury?

10 Now we can also look at the preliminary
11 results of the continued access study to see if the
12 mitigations are working, and so far there has been one
13 case of a patient with symptoms consistent with nerve
14 stimulation, and one case of nerve injury that
15 resolved two days post treatment. It's reported that
16 this patient experienced warmth down the right leg
17 during two to three sonications, and that one day post
18 treatment she felt her right foot hitting the ground
19 harder than the left, and she had stumbled once.

20 Now in conclusion, it appears that the
21 skin burns have been limited by additional training,
22 but nerve injuries have not been eliminated by

1 currently implemented mitigation methods. And while
2 we believe that the risk of nerve injury will not be
3 completely eliminated, are additional mitigations
4 warranted?

5 The attachment to the discussion questions
6 provides a listing of the mitigations implemented in
7 the pivotal and continued access studies. In the
8 discussions of Question 5, please also comment on
9 whether or not additional mitigations are warranted to
10 prevent unintended heating of the sacral and sciatic
11 nerves. This completes the FDA presentation, and I
12 turn it back to you, Dr. Noller.

13 DR. NOLLER: Thank you very much. Once
14 again, thank you for staying within the time allowed.
15 We have a few minutes now before lunch time, and
16 during this short period of time, what I would like to
17 do is to ask the panel if they have any questions that
18 they would like to perhaps pose to either the FDA or
19 the sponsor this afternoon. We won't discuss them
20 now, but if we present the questions now, it will give
21 them a chance to think them over, and develop some
22 answers.

1 I'm going to take the Chair's prerogative
2 and ask my questions first so I get them all in.
3 First of all, I'm curious - and this is a question for
4 the sponsor - I wonder if you have an explanation for
5 the variability between the dose volume and the non-
6 perfused tissue volume. You stated it was not blood-
7 flow dependent. From the charts we saw that the FDA
8 presented it wasn't consistent either. If it were
9 always 1.5 times the volume or 2.3 times the volume,
10 you could make calculation, but it varied all over the
11 place. And if you could try to explain that to me.

12 Secondly, in the material we received, and
13 this goes along with safety and education, I didn't
14 see any teaching about conscious sedation. You might
15 have thought that's not necessary because hospitals
16 have rules, but this is an out-patient procedure that
17 could be done in a free-standing place where that
18 wouldn't be required, so are you going to include
19 that?

20 And last, is there any sort of lockout
21 feature that prevents providing pulses closer together
22 than every 90 seconds as you now have them set up? If

1 somebody is in a hurry, they have to get to their golf
2 game, could they do pulses every 15 seconds and cause
3 damage, or do you have a lockout feature. Yes, sir.
4 Dr. D'Agostino.

5 DR. D'AGOSTINO: I have a few questions
6 which may have been covered but I missed them. The
7 first one is the symptom severity scale. We talked
8 about validation. Is there a literature that I've not
9 been able to find that talks about a change of 10
10 points as being some high level of clinically
11 meaningful change?

12 My second question is that I'm struck by
13 the control group, that I would have thought the
14 adverse events that the hysterectomy group was going
15 to be observing would be somewhat different than what
16 this new treatment is. And you may have said it, but
17 what was the actual logic? I heard a lot of negatives
18 on why you had to get a control group, and you ended
19 up picking hysterectomy, but I don't hear any
20 positives on how you could really make these sort of
21 safety comparisons, especially on the issues that are
22 relevant to the ExAblate.

1 And then my third question is that the
2 symptom severity scale in the baseline versus the
3 screening seemed to have on the data that was
4 presented, that you almost had like 20 percent or so
5 of the subjects changing by a score greater than 10.
6 And I'm concerned when you get to the year, you have
7 about 40 subjects who are positive, meaning greater
8 than 10; where if you just took repeated measures you
9 may have had something like a change of 10 out of
10 those 20 just by chance alone. And so I'm concerned
11 about how I'm supposed to interpret the 12 month
12 results given the variability in the scale, and also
13 the fact that you only designed a six month follow-up,
14 and how is the panel supposed to respond to that?
15 Thank you.

16 DR. NOLLER: We'll go to Dr. Brown and
17 then Dr. Crum, then Dr. Miller.

18 DR. BROWN: My questions are really all
19 for the sponsor. I have a question about and a
20 concern - we talked a lot about the risk to the sacral
21 plexus and sacral nerves. And from my knowledge of
22 anatomy and review of the materials, it seems to me

1 that the colon and rectum are going to often be
2 included, if not almost always included in the post
3 focus point beam. And I wanted to get a little more
4 detailed information about exposure of the colonic
5 mucosa serosa to the post focus beam energy and the
6 effects that may be have seen in the patients in terms
7 of GI symptoms. And also, there was some discussion
8 about air stopping the beam. Was there any
9 consideration given to patients having an empty rectum
10 at the time, and is that being looked at in the
11 ongoing study?

12 Second question is what provisions were
13 taken and will be recommended, particularly in the
14 training, to ensure that the abnormalities were being
15 looked at in MRI are actually fibroids and not some
16 other entities such as a sarcoma or adenomyosis?

17 Third question is, who are the intended
18 potential practitioners? Is this intended to be used
19 only by radiologists? Is it intended to be used by
20 practicing OB-GYN physicians. And again, I didn't
21 really glean that from any of the materials.

22 Another question for me is one of my more

1 important questions. What are the implications of the
2 fact that only 11 percent of your treatment group in
3 the pivotal study were African American women, only 1
4 percent Latino, 3 percent Asian, no Native American or
5 Native Hawaiian women. What are the implications of
6 this to the generalizability of your results in the
7 population in the United States? As we all know, the
8 group who would probably most benefit from this
9 treatment and have the highest incidence of
10 symptomatic fibroids are African American women, so
11 could you comment on that? That's about it.

12 DR. NOLLER: Dr. Crum.

13 DR. CRUM: This is for the sponsor. In
14 your panel package, a statement was made, "The ability
15 to predict the ablated tissue volume as a result of a
16 given sonication is the central factor upon which the
17 entire treatment plan is based", so this issue of
18 predicted thermal dose area versus non-profuse volume
19 I think is the central issue there.

20 And it seems to me that the fault is in
21 the thermal dose prediction in the model, and I would
22 like to ask because I couldn't determine it from our

1 package, in the thermal model do you consider
2 temperature dependent attenuation, because the
3 attenuation can go up by a factor of 50 to 75 percent
4 during a temperature elevation, frequency dependent
5 attenuation, because if you have a water path in
6 front, you get non-linear effects, which means you get
7 higher frequencies. And those are -- those
8 attenuations are frequency dependent.

9 No perfusion I could see in the model. No
10 long linear effects, as I mentioned earlier, and no
11 cavitation. That's a difficult issue, but cavitation-
12 related heating is, of course, in the recent
13 literature a very important factor, so I'd like the
14 sponsor to address that.

15 The second thing following on the point of
16 cavitation is there is some statements, page 35 I
17 think, that says that the threshold for cavitation is
18 approximately 1,300 watts per centimeter squared, D-
19 rated. The intensity would be on the order of 800, so
20 that's significantly below the threshold for
21 cavitation, but on the other hand, that data from
22 Hynynen was based upon pulsed cavitation, pulsed

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1 acoustic protocol. And it also was done at a fixed
2 temperature. The temperature at 85 degrees, the
3 threshold for cavitation is significantly less, of
4 course, than 1,300 watts per centimeter squared.

5 I know you have a cavitation detection
6 system that was never mentioned, and I'd like to see
7 how that works, and if it works. Thank you.

8 DR. NOLLER: Dr. Miller.

9 DR. MILLER: Yes. My questions are also
10 directed to the sponsor. I'm interested to know in
11 the primary pivotal study why a non-randomized design
12 was chosen. And I again I may have missed it, but I
13 don't see enough address of the differential in the
14 study populations since it wasn't randomized. And the
15 specific issues that I'm interested in are these
16 populations differed, as we've already heard, by race.
17 I don't find any report of the number of fibroids in
18 the TAH group, or the volume assessments of those
19 fibroids, and how they compared.

20 Also, in terms of the calculation of
21 disability, there's a lot of analysis relative to the
22 differential in calculated disability, but if you

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1 consider that 33 percent of the focused ultrasound
2 group needed to be retreated, some of whom were then
3 treated by hysterectomy and other modalities, there
4 doesn't seem to be any aggregate calculated disability
5 that would include complete treatment, particularly
6 when you're looking at outcomes over a six and twelve
7 month period.

8 In terms of the health-related quality of
9 life scale, and this again gets back to the
10 differential in the populations, if I read this right,
11 there was a significant prevalence of underlying
12 depression in the TAH group, which wasn't reflected in
13 the focused ultrasound group. And there were some
14 other differential characteristics, like anemia and
15 hypertension, what medications were they taking for
16 their hypertension? Again, these all speak to the
17 fact that these populations were very different. And
18 since you're basing your efficacy on this 10 point
19 scale, what analysis can be deployed to understand the
20 comparison?

21 And the final thing that I want to ask you
22 about is what post hoc analysis was done to better

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1 understand the treatment failures in the focused
2 ultrasound group? Clearly, it's a significant
3 population. Obviously, I would think that you'd want
4 this to be a modality that would be effective for the
5 long term. Can we have any better understanding of
6 what patient population is this better designed for,
7 and maybe that would inform the exclusion criteria in
8 the future. Thank you.

9 DR. NOLLER: We have about eight more
10 minutes and five people. Dr. Hillard, you were first,
11 then Dr. Brill and Dr. Solomon, Dr. Diamond.

12 DR. HILLARD: Questions for the sponsor,
13 questions about the patient death. Was an autopsy
14 performed on that patient? What were the findings,
15 particularly the findings in the pelvis for this
16 patient? And given that she did clearly have
17 additional risk factors, are there any screening
18 issues that could be recommended. If you had known
19 she had Factor V Leiden, could or should this have
20 been an exclusion for treatment?

21 In follow-up of the questions about who is
22 the intended practitioner, if this is a radiologist,

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1 what recommendations would be given for communication
2 between the gynecologist and the radiologist in terms
3 of both follow-up, and also in terms of immediate
4 potential for complications, the potential for acute
5 bowel injury or intra pelvic hemorrhage, so these need
6 to be addressed in the planned training and
7 recommendations.

8 DR. NOLLER: Dr. Brill.

9 DR. BRILL: Yes, I have a number of
10 questions. First query regarding inclusion or
11 exclusion and the follow-up. For what reason FSH was
12 not followed in the patients after therapy? And I
13 wondered if there's any stratified data regarding the
14 effect of this and oral contraceptives which appears
15 to be acceptable in the protocol in the patients after
16 treatment.

17 In regards to the myoma treatment itself,
18 if I'm reading the materials correctly there were a
19 number of myomas of 2.3 per patient, and a mean number
20 of treated 1.3. So the question is what method was
21 used to choose which fibroids were to be treated,
22 number one. Number two, what was used to rule out the

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1 fact that they may be degenerated already, and why
2 were non-perfusion volumes not applied before the
3 institution of the protocol?

4 And third, Dr. Stewart, you mentioned that
5 those amenable to hysteroscopic or laparoscopic
6 myomectomy would not necessarily have been treated,
7 and I'd like to know more details about that statement
8 regarding the pivotal trial.

9 And last, regarding the non-perfused
10 volume - we heard a number of references to the point
11 that in fact the NPV appears to under-estimate the
12 histology. Well, if that's the case, if we take the
13 statistics that were presented with a non-perfused
14 volume of average of 68.7 Ccs and a percent of the
15 myomas treated 23.6 percent, then how at six months do
16 we have a 14 percent shrinkage, and thereafter, a 9.4
17 percent shrinkage from the intent-to-treat, if indeed
18 the area was greater than treated versus less.

19 DR. NOLLER: Dr. Solomon.

20 DR. SOLOMON: In the material presented to
21 us, the test arm inclusion criteria include MR
22 accessible fibroids, but there isn't a discussion as

1 to how many patients were rejected because of
2 interrupted -- intestines in the pathway of the beam
3 or calcifications in the fibroid, so that there are a
4 number of patients that were obviously excluded, and
5 we don't have a good sense of that in the materials.

6 Secondly, the beam pathway can be affected
7 by interactions or interfaces between different
8 tissues. And the beam then can be in a different --
9 the focus can then be in a different place from where
10 the predicted focus would be, and that's part of the
11 calibration procedure early in the program here. The
12 question is how often is the sub-lethal dose different
13 from the actual focus, and how far do you have to move
14 it, because that may be something that comes up in
15 other parts as you move the focus around, that you
16 could be endangering other tissue.

17 And the third question is, we have in here
18 the use of MR thermometry in order to mitigate the
19 risk of unnecessary heating of critical structures,
20 but it appears that in the case of the skin and the
21 nerves that MR thermometry safeguard was unable to
22 succeed, and so maybe further discussion there would

1 be helpful. Thank you.

2 DR. NOLLER: Dr. Diamond.

3 DR. DIAMOND: I had a number of questions
4 actually about the logistics of how the study was
5 conducted. First of all, you said that the decision
6 was made to use a 3-2 ratio for randomizing patients
7 or assigning patients in the treated arm or in the
8 control arm, but why was that -- what were the
9 demographics that were utilized to come up with that
10 power calculation, and the idea to use that ratio?

11 The evaluation of the perfused area, like
12 Dr. Brill, I wondered was that done before the study.
13 It's my understanding it was. What percent was not
14 perfused at that point, or were they all totally
15 perfused if they were going to be included in the
16 study. Was the -- obviously, the practitioners, the
17 radiologists were making that assumption in the
18 decision at the time of the study, but was that the
19 actual data that was utilized for the calculations
20 that we see here, or was the ultimate data that we've
21 seen here generated from a central review of perfused
22 and non-perfused areas. If it was not, how was that

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1 standardized between different investigators. And did
2 the individuals doing it, if it was central site, did
3 they know whether it was initially procedure,
4 immediately post procedure, or at later time points,
5 because without a control group which has those sorts
6 of measurements, I think there's a potential for bias
7 knowing that it's potentially treated; and, therefore,
8 subconsciously thinking maybe it should be either
9 larger or smaller, whichever that could potentially
10 go.

11 You've given us the change in fibroid
12 volume and perfusion volume. You didn't give us the
13 uterine volume changes though, and I'd be very
14 interested to know that, typically since you're
15 treating just 1.2 fibroids in these patients.

16 It's also very curious to me that with the
17 small percent change that you saw in the fibroid
18 volume, that you saw the benefit that you did see.
19 That's one of the reasons why I want to have the total
20 uterine volume changes, but do you have any idea why
21 such a small change in what I'm assuming will be total
22 uterine volume would have the beneficial effects that

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1 you did identify?

2 Other logistic issues, you mentioned the
3 thermography is measuring temperature change, and have
4 you done the standardized temperature of the patient
5 or temperature of the room? Have any studies been
6 done in other animals that have uteruses like humans,
7 like primates, with thermistors to see whether the
8 ultrasound treatments -- what sort of temperature
9 changes are seen there, and how well that is picked up
10 with all the modeling that's been shared with us,
11 whether that correlates or does not.

12 It appears to me that, at least as I've
13 read the documents, that some of the patients that
14 were in initially treated ended up being found out
15 that have adenomyomas and, therefore, were excluded
16 from the analysis, although they had already been
17 treated. Since that's likely to happen in clinical
18 practice, as well, the practitioners were not able to
19 differentiate initially, I'm not sure that's the right
20 thing to do. Similarly, I'm not sure that it's
21 necessarily appropriate to exclude those patients who
22 are outside the window when they had their follow-ups,

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1 and would like to see data as to how that might affect
2 uterine volume changes in those individuals.

3 The question came up is if you have
4 multiple fibroids, which one was treated. I'd also
5 like to know where within the fibroid was treated, and
6 how that was decided, and whether that has any impact?
7 Perhaps was it closer to the uterine surface, the
8 middle, or what location.

9 And then the question --

10 DR. NOLLER: Last question.

11 DR. SOLOMON: Last question. Another way
12 to assess the effect of the sonication might be
13 functional MRI looking at blood flow changes, and has
14 that been done?

15 DR. NOLLER: Thank you. One quick
16 question.

17 MR. WEEKS: If I may, three really brief
18 questions.

19 DR. NOLLER: Ten seconds each.

20 MR. WEEKS: First, the difference between
21 the thermal dose area and the non-prefused area, have
22 you looked at the relationship between that variance

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1 and BMI?

2 As far as your questionnaires for symptoms
3 as a tool, two questions. Was the timing of the
4 questionnaire, the taking of the information any way
5 related to where the patient was in her menstrual
6 cycle? And third, has there been any data on the
7 particular tool with regard to placebo effect? So for
8 example, has the same tool been used in medical
9 studies where there's been a prospective randomized
10 placebo control trial, and what is the magnitude of
11 placebo effect? That's it.

12 DR. NOLLER: All right. Obviously, we
13 don't expect you to respond to all of those. We'd be
14 here for all week. And we will not be asking you to
15 respond to all of them, but those are the sorts of
16 questions we have that may come up in our discussions
17 of our nine questions. But if you could prepare short
18 one or two sentence answers to some of those, and some
19 of them won't be asked, I'm sure, because the
20 questions won't directly affect that.

21 We will meet back here at exactly 1:00.
22 For the panel members, there's a place in the back of

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1 the restaurant for panel members only, and I have a
2 message here I don't understand. Why don't we do
3 those as we come back in our open panel discussion,
4 doing that, because I think a lot of people have more
5 questions. One o'clock, it's now 12:01.

6 (Whereupon, the proceedings in the above-
7 entitled matter went off the record at 12:01:35 p.m.
8 and went back on the record at 12:59:47 p.m.)

9 DR. NOLLER: During intermission we worked
10 out a couple of things here. I know there are other
11 panel members that had questions. We'll try to get to
12 everything today. We certainly don't want to cut
13 discussion short, but I think what we'll do for the
14 next little bit, we have now panel discussion from 1
15 to 2:45. We're going to ask the sponsor to respond to
16 the questions that they had in general categories.
17 And they said they can do that in about 10 minutes.
18 At that point, we will start our discussion of the
19 nine questions. And the work we have to do this
20 afternoon is to develop some answers to those nine
21 questions, and develop an overall opinion concerning
22 the approvability.

1 The open public hearing from 3 to 3:30, we
2 know that there will be at least one person to speak
3 then, so I ask the panel to watch the time and the
4 length of comments, questions, et cetera, but we will
5 go until we're done. We hope that go until we're done
6 is 4:30. Is the sponsor prepared to respond?

7 DR. STEWART: Thank you, Dr. Noller and
8 panel. What we tried to do is get some of the areas
9 of maximum overlap in terms of questions. And while
10 we'll be here to answer all questions. Our beepers
11 and cell phones are locked away in the suitcases, so
12 if we missed your question on the first round, we'll
13 clearly go back to it. But it appeared to be a
14 cluster of questions around the primary efficacy
15 endpoint, and why the symptom severity score was an
16 appropriate measure, was the 10 points the appropriate
17 measure, was there too much variability inherent in
18 this measure. And I think we chose this as a primary
19 efficacy endpoint because symptomatology is really the
20 primary complaint for women with fibroids. And that
21 this is significantly impairing their lives.

22 We chose the only fibroid-specific

1 validated measure. Again, it's a shame that the field
2 is so far behind in measuring disease impact for
3 women, and it wasn't until the last several years that
4 there was, indeed, a validated study. And so the
5 symptom severity score of the UFS-QOL is really the
6 appropriate measure for this disease.

7 Several people raised the issue of why 10
8 points, and if we can go back to one of the slides
9 that was in my presentation this morning, I know we
10 had a lot of different things over the morning, but
11 the 10 points was defined at the outset of the study
12 for two very different reasons. First of all, we
13 believed that it meant that there was clinically
14 significant improvement, that if we can get the graph
15 up eventually, if you'll recall, when they were
16 validating this questionnaire, the women with fibroids
17 had mean scores about 40, and women without fibroids
18 in the normal population had mean scores in the 20s.
19 So 20 points separated significantly effected
20 individuals from non-effected individuals.

21 And just like with other treatments for
22 fibroids, such as GNRH Agonist, if you get a 50

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1 percent volume reduction or a 50 percent reduction in
2 bleeding, this is generally clinically significant.
3 So for that, reason we chose 10 points.

4 Here we go. Do we have the pointer again?
5 So it's the two bars on the left, the symptomatology
6 and the fibroid bars are in blue with a mean of 44.
7 And the normal women were at 23. And, in fact, what
8 we found from our data was not that 10 points
9 separated our groups, but a mean of 23.8 points
10 separated our group. So again, if we look at the
11 differences that would bring the fibroid patients
12 really down into the normal range.

13 So if we had set our criteria for success
14 instead of at 10 points where we got 70 percent of
15 patients to respond, and we had hypothesized that
16 there would be 50 percent of patients, even if we move
17 that up to 15, we had 70 -- we would have 50 percent
18 of our patients having improvement. And we found,
19 again, a 40 percent reduction in symptoms which again
20 from our previous experience with drugs such as GNRH
21 Agonist or Mifepristone generally does translate into
22 symptomatic improvement.

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1 We also chose this cut-off for several
2 methodologic reasons, and if we can go back to the
3 word slide in terms of statistical methodology that 10
4 points was very close to the standard deviation of the
5 population very near to the standard there or the
6 mean, and it correlated with a moderate effect size.

7 The other issue that had been raised by
8 several individuals was that there was a variation
9 between the screening that we obtained on this
10 questionnaire at the screening visit, versus the
11 baseline at the treatment visit. And we went back to
12 look at those issues to assess what the differences
13 were.

14 It turns out that the treatment day
15 assessment of symptom severity and the follow-up ones
16 are very consistent. It was really the screening day
17 that showed variation. And in trying to understand
18 that difference we looked at several things. We
19 looked at difference to menstrual period and the
20 menstrual cycle. Cyclicity didn't seem to make any
21 difference.

22 What we found out was that there were some

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1 centers that were not administering it in the standard
2 format. As you may know, quality of life
3 questionnaires really do depend on you using the same
4 instrument in the same way. And some of the
5 recruitment centers, especially ones that had patients
6 coming in from long distances would sometimes use fax
7 copies or phone interviews to try to assess
8 symptomatology.

9 So we then were able to look at that. We
10 also found that there really wasn't any difference in
11 which measure we looked at. Both the median and the
12 mode of the differences were zero, and if we assessed
13 values between screening and six months versus
14 baseline and six months, we got the same difference.
15 So I think although it is a concern, it doesn't affect
16 the results, and this has proved to be a dynamic
17 measure.

18 There was also question about whether this
19 could represent a placebo effect. And although any
20 self-reporting measure is vulnerable to a placebo
21 effect, the first thing is that we do have clear
22 documentation that we had an effect. We have the

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1 radiographic imaging. We see the differences in blood
2 flow, and everyone did, indeed, have an MR image prior
3 to treatment that showed that there was enhancement.
4 That was one of the inclusion criteria.

5 We also know that size is not the only
6 criteria for efficacy. The questions were raised
7 about why we didn't get more size reduction, and I
8 think the UAE experience has told us that size
9 reduction doesn't necessarily correlate with symptom
10 reduction. And there are many changes that may be
11 going on in the consistency or the density, having a
12 lead ball sitting on your bladder may be very
13 different from having a cotton ball sitting on your
14 bladder and the size reduction doesn't have to factor
15 in.

16 Finally, although there may have been some
17 placebo effect at three months, that at six months I
18 think we were seeing a real effect. We got some
19 patients who would maybe see symptomatology relief at
20 three months, and by six months it was pretty clear to
21 any of us that spoke to the patients that they clearly
22 knew they were using less tampons or getting up less

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1 at night to urinate, or they weren't, and I think that
2 goes in general timing with the known information
3 about placebo effects.

4 And finally, we had multiple parameters
5 that were consistent. We didn't just rely on the
6 symptom severity score. We had SF-36 monitoring to
7 prove that we were getting concordance in our study
8 sample. We also had health-related quality of life
9 and overall treatment effect, as well. Is that my 10
10 minutes?

11 DR. NOLLER: It is.

12 DR. STEWART: Okay. Is there any
13 questions?

14 DR. NOLLER: Thank you.

15 DR. STEWART: Okay.

16 MR. NEWMAN: If there's any of the
17 questions that were asked earlier that need to be
18 covered before the deliberation, we'd be glad to cover
19 those.

20 DR. NOLLER: We may ask you back up to the
21 podium as we go along here, you and/or the FDA. Okay.
22 That was 10 minutes. Is the company okay with that?

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1 That's what you asked for, that's what you got. Are
2 you --

3 MR. NEWMAN: We said we believed in 10
4 minutes we could cover the main topics that had been
5 covered by several people. Of course, that left many
6 other questions unanswered, the physics questions and
7 some of the other more specific things, and we'd like
8 to cover those before we get to the deliberation and
9 vote.

10 DR. NOLLER: Okay. That sounds good.
11 What I'm going to do now for the panel is to read you
12 three definitions. The definitions of safety,
13 effectiveness, and valid scientific evidence. These
14 are the measures that we are supposed to use in making
15 our decisions today.

16 Safety, the definition reads: "There is a
17 reasonable assurance that a device is safe when it can
18 be determined based upon valid scientific evidence
19 that the probable benefits to health from use of the
20 device for its intended uses and conditions of use,
21 when accompanied by adequate directions and warnings
22 against unsafe use outweigh any probable risk."

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1 Definition of effectiveness is: "There is
2 reasonable assurance that a device is effective when
3 it can be determined based upon valid scientific
4 evidence that in a significant portion of the target
5 population, the use of the device for its intended
6 uses and conditions of use, when accompanied by
7 adequate directions for use and warnings against
8 unsafe use will provide clinically significant
9 results."

10 And then finally, the definition for valid
11 scientific evidence: "Valid scientific evidence is
12 evidence from well-controlled investigations,
13 partially controlled studies, studies and objective
14 trials without matched controls, well-documented case
15 histories conducted by qualified experts, and reports
16 of significant human experience with a marketed device
17 from which it can fairly and responsibly be concluded
18 by qualified experts that there is reasonable
19 assurance of the safety and effectiveness of the
20 device under its conditions of use. Isolated case
21 reports, random experience, reports lacking sufficient
22 details to permit scientific evaluation, and

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1 unsubstantiated opinions are not regarded as valid
2 scientific evidence to show safety or effectiveness."

3 MS. BROGDON: Dr. Noller, I'm sorry to
4 interrupt.

5 DR. NOLLER: Yes, ma'am.

6 MS. BROGDON: I just have a procedural
7 question. The panel laid out a number of questions
8 for which you'd like answers from the firm. I'm just
9 not clear on when you intend the firm to be able to
10 answer those questions.

11 DR. NOLLER: I think those that were not
12 answered will come up as we go through these
13 questions, and we will give the sponsor time as we go
14 through the questions.

15 MS. BROGDON: Okay. Thank you.

16 DR. NOLLER: And certainly before we do
17 our voting. The first group of discussion questions
18 are six, and they deal with safety and effectiveness.
19 And the first is the primary effectiveness endpoint
20 for the pivotal study is the symptom severity scale
21 derived from the uterine fibroid symptom and health-
22 related quality of life questionnaire. Success was

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1 defined as a 10 point improvement in the symptom
2 severity scale of the UFS-QOL instrument in at least
3 50 percent of ExAblate patients at six months. Is the
4 10 point improvement at six months a clinically
5 meaningful measure of success?

6 As we go through these, I will ask our
7 primary reviewers, Dr. Diamond and Dr. Roberts, to
8 start the discussion of each one of these points. Dr.
9 Diamond.

10 DR. DIAMOND: At this point, I guess I
11 remain unconvinced that a 10 point drop here was a
12 clinically significant difference. It seems like this
13 group of patients is a very select group of patients
14 with uterine fibroids. We were told that they were
15 not amenable to hysteroscopic treatment. They were
16 not amenable to laparoscopic treatment because those
17 patients would have been treated in those fashions.

18 Furthermore, the average hematocrit of
19 these patients I think was about 37 to start with, and
20 so there are a group of patients who have fibroids but
21 are not overly or imminently symptomatic, at least as
22 the data has been presented to us. If you had

1 included some patients who have greater symptoms,
2 greater amount of bleeding, then the original score in
3 the fibroid group might have been more than 40, and
4 the differences going back to a normal patient
5 population may have been 30 or 40, which would have,
6 as the company has presented to us, would have
7 influenced what they were seeing as a clinically
8 significant difference because they were looking at
9 standard deviation or standard error, or half the
10 distance from where the treatment group was to the
11 control patients in the validation study which
12 described the use of this instrument.

13 And I guess the last component I'd want to
14 make about that comment is, as I read the manuscript
15 which was presented to us in our packet, that
16 manuscript describes a difference between patients
17 with fibroids and patients without fibroids, as to
18 what you would expect to see on the scores, and that
19 data was presented to us. But that manuscript does
20 not talk about at all any sort of changes, or what is
21 a clinically significant change for that instrument.
22 So while it's been validated, differences for patients

1 with fibroids as opposed to without, I'm not convinced
2 that it's been validated for changes of symptoms for
3 patients who are having treatments for fibroids.

4 DR. NOLLER: I'll say just as an side, I
5 understand that at the open public hearing we will be
6 getting some more information about the instrument
7 that was used from a public member who -- from a
8 person in the audience who will speak. Would you
9 like to respond, sir?

10 MR. NEWMAN: Chairman Noller, can we
11 respond to that question?

12 DR. NOLLER: Yes.

13 MR. NEWMAN: That was one of the
14 questions, we didn't cover that in our 10 minutes.

15 DR. STEWART: I think that it is clear
16 that the patients that we saw were significantly
17 symptomatic, that if you look at again our symptom
18 severity score, we were well in excess of what was
19 defined as a mean level of symptoms for women in the
20 validation study. We were looking at a mean of 40,
21 and our patients in the MRI guided focused ultrasound
22 group had a mean of 61, which was very similar to the

1 mean of 69, I believe, in our hysterectomy group. So
2 although they may not have had significant anemia,
3 they did, indeed, have significant fibroid symptoms.

4 They also had a significant uterine
5 volume, that the mean uterine volume was 600 cubic
6 centimeters, and with the standard deviation there
7 were patients in this population that had well over
8 1,000 cubic centimeters, so I would agree that they
9 didn't overlap the patients for whom we would perform
10 a hysteroscopic myomectomy or a laparoscopic
11 myomectomy, but they clearly were the patients who
12 would currently undergo an abdominal myomectomy, a
13 hysterectomy, or in many institutions a uterine artery
14 embolization.

15 DR. NOLLER: Thank you. Dr. Roberts.

16 DR. ROBERTS: Well I had some of the same
17 concerns because when I -- to some degree I think have
18 been answered, but when I went through the paper
19 looking at the quality of life measurements, and I
20 went through other papers that talked about looking at
21 quality of life, I couldn't find anywhere that 10
22 points meant anything, so you've somewhat answered my

1 question in terms of whether or not that's a realistic
2 goal. I don't think we really have a good answer for
3 it.

4 I was impressed, though, when I looked at
5 that, that in comparison to the group where there was
6 in the validation study where the patients with
7 uterine fibroids certainly had a -- the patients in
8 this group had a much more of a severity index than
9 those patients, so they obviously were quite
10 symptomatic.

11 The one thing that I was little bit - a
12 little bit off the subject of this - but one of the
13 things I was a little bit confused about in terms of
14 the study was, I didn't find anything anywhere that
15 indicated what were the primary symptoms of these
16 patients. In other words, were most of them coming in
17 with bleeding, were most of them coming in with both
18 symptoms? When you look at the anemia levels, unless
19 they're doing pretty well on keeping up on their iron
20 levels or something, and being able to keep up with
21 their blood less, you would have to say that maybe
22 most of them were bulk symptoms. But I think that's

1 very important because when you look at some of the
2 patients that then go on to have hysterectomies or
3 drop out of the study, you get the impression that
4 many of these are for bleeding problems. And maybe I
5 missed it, but I just couldn't find it in there to
6 indicate what it was that these patients were coming
7 in with.

8 DR. NOLLER: Let's hold off just a second,
9 get other comments, and then we'll ask you. Any other
10 panel discussion on this number one? Yes, Dr.
11 Hillard.

12 DR. HILLARD: Just in thinking about
13 whether 10 points is clinically meaningful or not, one
14 could just mathematically come up with a situation in
15 a patient who is maximally symptomatic, so answering
16 five at the far extreme of the scale for all of the
17 symptoms, and could with only half of those symptoms
18 drop down to having symptoms a great deal. And that
19 would be a drop of over 10 points, so if you ask me if
20 that's a clinically significant improvement, she still
21 has symptoms a great deal of the time for many of her
22 symptoms, so I think that mathematically I have -- in

1 theory that would not qualify as a success. And so,
2 therefore, I wonder about having some sort of an
3 absolute value in addition to a magnitude of decline.

4 DR. NOLLER: Dr. D'Agostino.

5 DR. D'AGOSTINO: I was just going to say
6 in terms of when I'm involved with these type of
7 scales, the validation with the change, you'd like to
8 see the group move to some other clinically relevant
9 group. And they're moving to 40, which is sort of
10 what the original comparison group was with the
11 normal, so it's hard to figure out I think what the 10
12 means, and even where they moved into.

13 I do also think that if they got very
14 extreme individuals, it tends to be on the scales, the
15 ones that are extreme tend to change the most. And I
16 don't remember the way the comment is, but I don't
17 know what's driving the scale, and what the 60 to 40
18 actually means in terms of the clinical symptoms, and
19 is that really clinically exciting? And I think we're
20 missing that by just putting everything into a number
21 like 10.

22 DR. NOLLER: Dr. Brown.

1 DR. BROWN: Another question that I hadn't
2 asked was, which I didn't find, was what were the
3 percentage of the patients that hysterectomies that
4 had a 10 point change? Because to me, that would give
5 me some perspective to gauge again, so we say that 100
6 percent of the patients that had hysterectomies had a
7 10 point change, that would mean one thing. If you
8 said 30 percent of them had a 10 point change, that
9 would mean another thing, so I thought that bit of
10 information would be helpful, and I wasn't able to
11 find that anywhere. I don't know if that could be
12 addressed.

13 MS. MOONEY: If I understood the 10 points
14 correctly, I think in looking at the validation or the
15 comparison between fibroid patients and normal
16 patients, the scales we looked at earlier, it was a 40
17 to 20 drop, so the 10 points there represented a 50
18 percent change. And I think, if I'm reading this
19 correctly, from the six month data, it looks like
20 baseline for the intent to treat patients was 61 as
21 was just mentioned, and dropped to 34. So I think in
22 terms of that 50 percent improvement for this patient

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1 cohort, it seems fairly similar to that 40 to 20. So
2 I think the 10 points was not so much an absolute
3 number. It was chosen, if I'm understanding
4 correctly, but it represented a 50 percent change from
5 fibroid patient to normal patient.

6 DR. NOLLER: Dr. Janik.

7 DR. JANIK: I think six months is very
8 short. We need to really look out a little bit
9 farther to see if there's a risk gain that's
10 beneficial. To take any risk for a six month
11 temporary improvement is similar to medical
12 management, so we have to go beyond that, and also
13 correlate with how many people go on to have
14 hysterectomy. It's too short.

15 DR. NOLLER: Yes, Dr. Solomon.

16 DR. SOLOMON: One of the things I'm having
17 trouble with on the scale is the meaning of all of
18 this in absence of what I think the ideal control
19 would be, which would be to separate a placebo effect.
20 In this study, we wave all these fancy machines and we
21 tell the patient things went great, and they go home,
22 fill out a survey. And then you say well, how did you

1 do, and they want to please. And we don't have a
2 control here where maybe -- in any study I've seen,
3 this is the best one because you can do a sham
4 operation without having to put the patient through a
5 big incision. There's no real downside than taking up
6 some time. They can sit on the machine, the lights
7 flicker and they say hey, you got the treatment, and
8 then they get the survey later. I think something
9 like that would give meaning to a 10 point change
10 alone.

11 DR. NOLLER: Dr. D'Agostino.

12 DR. D'AGOSTINO: I was going to follow up
13 on the 12-month follow-up. They ran into trouble
14 because there weren't evidently designing a 12-month
15 study, but the 12 months certainly makes the
16 comparison or the numbers look a lot less exciting.
17 They're down to less than their 50 percent changing
18 over by a 10 point scale. And they also were in a
19 situation where they have a lot of individuals moving
20 to another procedure, and getting the hysterectomy,
21 and I did ask that as one of the questions. And I
22 really, if possible, to try to get a response from the

1 sponsor on that, because I don't see how we --
2 personally how I move out of the dilemma that I'm very
3 unimpressed by the 12 month data.

4 DR. NOLLER: I'm going to call on Dr.
5 Miller, and then I'm going to ask the sponsor to
6 respond to some of these items that have come up. Dr.
7 Miller.

8 DR. MILLER: Well, interpreting the
9 success or the meaning of the value of that 10 point
10 drop, I mean I think we have to understand it in terms
11 of the real attrition of this population. So if 12
12 months is a meaningful endpoint, at that point we only
13 are dealing with 44 patients that we have data for.
14 We've lost over 60 percent of our sample, and I think
15 that makes the question of bias, and who stayed in,
16 and whether people who actually felt better about
17 their treatment; in other words, were maybe less
18 symptomatic to begin with, were more satisfied to
19 begin with, and were still in the study. So that 10
20 point as a reference point is material in terms of who
21 stays in the study when you have an attrition rate
22 that's that high.

1 DR. NOLLER: In fairness to the sponsor,
2 too, let me remind people what we said earlier, that
3 originally there was some misunderstanding, I guess,
4 in the length of follow-up, so they didn't recruit
5 these people to be followed for a year, so they had to
6 go back and find some of them, and so there was some
7 additional loss that normally we wouldn't expect.

8 Everyone who comes to the microphone from
9 now on, even though you've spoken before, please give
10 your name as we're recording this, so they have the
11 name. So does the sponsor want to respond to some of
12 these issues?

13 DR. STEWART: I'm Ebbie Stewart, and it
14 sounds like there's still concern about the 10 point
15 threshold. That clearly at the outset of the study,
16 it was a hypothesis that this was an important
17 difference. I think there are good methodologic and
18 clinical reasons to suppose that this is an important
19 endpoint, but I think, in fact, we saw substantially
20 better improvement than that. We found 24 points on
21 average, and many patients improved 30 or 40 points on
22 this scale.

1 I think we also got objective endpoints in
2 terms of by a reduction in terms of comparability to
3 the treated endpoint, and outcomes on SF-36. I think
4 also some of the concerns addressed the control group,
5 and I would love to be able to tell you we could
6 perform a randomized study. I think at the outset of
7 this, there wasn't any way that we could feasibly
8 perform a randomized study that we didn't have a
9 minimally invasive treatment that had FDA approval.
10 We had, ourselves, the experience of randomized, or
11 trying to get people to trade-off between this
12 minimally invasive procedure and an open procedure,
13 and had seen what had happened with the attempts to do
14 the same thing for uterine artery embolization. So
15 we, therefore, chose the most comparable group we
16 could find, and I think that the women in our study
17 were indeed women who would have qualified for
18 hysterectomy in any institution.

19 We weren't able to blind people to this
20 treatment modality, and I think that we have
21 established that we did get significant efficacy with
22 these patients, that there are very significant

1 clinical improvements that we have seen.

2 There's other investigators here that may
3 be able to give their input since you've heard a lot
4 from me. I'll introduce you to one of our other
5 investigators.

6 DR. NOLLER: Please limit to about a
7 minute.

8 DR. GOSTOUT: Okay. In one minute. I'm
9 Bobbie Gostout, and I'm from Mayo Clinic, and I'm a
10 consultant for InSightec, but I do operate under the
11 guidelines of Mayo Foundation, and under the
12 guidelines of IRB at Mayo Foundation. And I should
13 state just to be clear that my travel and
14 accommodations here were provided by InSightec.

15 A couple of things to just briefly wrap
16 up. Some people are saying well, maybe if the
17 patient's initial symptom scores were higher, we could
18 say more about what this means, and I'd just like to
19 point out that I believe we really are presenting to
20 you a spectrum of patients with a range of symptoms of
21 human fibroids that require treatment, which I think
22 makes it, if anything, the best study that we could be

1 presenting to you, rather than saying we only took
2 patients that were at the maximum on every symptom
3 possibility.

4 I'm hearing questions saying well, what is
5 the clinical significance of this reduction on this
6 symptom severity scale? I think it's important to
7 consider a couple of slides that we presented before
8 when we looked at patient satisfaction, and documented
9 that at six months the patient's satisfaction in terms
10 of saying that it was effective is, I believe, 72
11 percent. And at 12 months, we're looking at 79
12 percent. So the patients are telling us that the
13 difference that they're measuring on this objective
14 score means something to them. And in my mind, that
15 validates the clinical significance of this. They're
16 telling us that -- we asked them to put it in numbers
17 and make it objective, but they're telling us saying
18 I call this treatment effective. And, in fact,
19 American College of OB-GYN's recommendations are that
20 you treat uterine fibroids when they're a bother to
21 the patient. And the patients are telling us that we
22 effected the change that she came requesting.

1 If we go to a randomized clinical trial,
2 I would tell you that at least one-third of the
3 patients that I see that have entered into this trial,
4 it would probably be an ethical question whether or
5 not I could do a sham procedure for her, and in fact
6 do nothing for her symptoms, because really, in fact,
7 we are dealing with a number of patients that had the
8 severe type of bleeding that makes me concerned about
9 fainting episodes, that makes me concerned about them
10 driving or even caring for their children when they're
11 having their period, so we have a significant number
12 of patients that were highly symptomatic, and I would
13 be concerned about just randomizing them to no
14 effective treatment.

15 DR. NOLLER: Thank you. I'm going to go
16 on to the second question, because it also deals with
17 effectiveness. The intent-to-treat success rate at
18 six months was 70.9 percent as indicated in the table
19 below, and you all have that table.

20 The ITT success rate at 12 months was 40.4
21 percent. The success rate dropped in part due to
22 patient lost to follow-up between 6 and 12 months. By

1 12 months, approximately 20 percent of the ExAblate
2 subjects had undergone alternative treatment for their
3 fibroids. Secondary endpoints included fibroid volume
4 changes at 6 months. On average, the treated fibroid
5 volumes decreased by 16 percent. The question: Did
6 the patient reported outcome data from the quality of
7 life instrument at 6 and 12 months, when coupled with
8 the clinical result of actual volume reduction of
9 reduced fibroids support the effectiveness of the
10 ExAblate for the treatment of uterine fibroids? Panel
11 discussion. Yes, Dr. Diamond.

12 DR. DIAMOND: In order to put into
13 perspective for me the 16 percent drop in fibroid
14 volume, it would be very helpful for me to know some
15 of the things I asked for before the break, which was
16 when happened to total uterine volume before and
17 after? So was the 16 percent consistent with what
18 happened to total uterine volume going down, did it go
19 in the opposite direction of total uterine volume?
20 How were the readings done? Was it done by a blind
21 reviewer centrally, or controlled for potential bias
22 as to when it was being done; again, some of the

1 logistics of how the study was actually conducted to
2 get a better feeling for whether the 16 percent is --
3 how real that data is.

4 DR. NOLLER: Dr. Wood.

5 DR. WOOD: I'd like to make a point of
6 clarification on the 16 percent, and it relates to
7 thermal ablation therapies are often staged in cancer.
8 And in this case, followed with volumes, and it points
9 to the -- it's maybe not representing what you think
10 it is. And if you think about a tumor, or in this
11 case a fibroid, changing characteristic, becoming
12 soft, that's not represented volume, and overall your
13 thermal lesion, your effective devascularized
14 coagulative necrosis area is also represented in this
15 fibroid volume, as I understand it. So it's not
16 necessarily a very pertinent measure.

17 DR. DIAMOND: Well, it's what we're
18 presented with, and it's one of the markers that the
19 sponsor has put forward as a marker of efficacy.

20 DR. WOOD: I understand that. I just want
21 to clarify for the panel that this number is not
22 necessarily indicative of -- you're not talking about

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1 a fibroid that is just shrinking 16 percent. The
2 characteristics are shrinking and changing
3 potentially, and they're not representative of that
4 number.

5 DR. DIAMOND: That's true, but I don't
6 know of any information that suggests that the
7 characteristics of the fibroid, whether it spongy or
8 whether it's hard, where that's been documented to
9 show that that was associated with different symptoms
10 by the patients. I think that's relevant.

11 DR. WOOD: Speaking from cancer therapies,
12 we can treat a tumor, have it remain the same size.
13 We can partly treat a tumor and get symptomatic relief
14 that's long-lasting and not have the volumes change
15 whatsoever in the measurement, so that's why the cyst
16 criteria don't really apply to thermal ablative
17 therapies in cancer, for example. I know this is off
18 the subject, but the same sort of paradigm here may
19 not fit. It's just a point of clarification.

20 DR. NOLLER: Other comments from the
21 panel. Dr. Roberts.

22 DR. ROBERTS: Well, the only thing that I

1 would say is that certainly -- my experience has with
2 uterine artery embolization that even though you may
3 not get a huge decrease in the size of the fibroid,
4 the patients will tell you that there's something
5 different about the fibroid, even if it's more or less
6 the same size. But I do think it's -- I think that
7 there is some confusion, certainly in my mind, and
8 maybe the sponsor would be willing to look at this, or
9 to give us some information about that; and that is,
10 how does the change in the fibroid volume -- do you
11 have any documentation about the uterine volume at the
12 same time?

13 DR. NOLLER: Let me ask the sponsor here
14 to answer that. Do you have data on the total uterine
15 volume? And then the other question was were the
16 volumes and results blinded as to whether it was
17 treatment or not?

18 DR. TEMPANY: Yes. I'm happy to respond
19 to that. I'm Clare Tempany. The uterine volume was
20 measured at baseline, but it was never measured again
21 after that in the follow-up examinations.

22 DR. DIAMOND: Don't you have that? I mean,

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1 you've got the images.

2 DR. TEMPANY: Yes, but I don't have that
3 data to present to you now.

4 DR. NOLLER: Let's let them finish the --

5 DR. TEMPANY: We have the total fibroid
6 volume, and we have those numbers that we've shown you
7 already. And to go back to your other questions, Dr.
8 Diamond, about the measurements, and whether they were
9 done by single readers at single sites, or whether
10 they were done at a core lab. They were, in fact, all
11 done at the core lab with standardized interpretation
12 and measurements ahead of time by a single person.

13 DR. BAILEY: And was that reviewer blinded
14 to whether it was a pre, or a six month, or a twelve
15 month evaluation?

16 DR. TEMPANY: No, I believe they knew
17 which examination it was. They knew it was baseline,
18 they knew it was six months. And then the other
19 questions you had asked, just to clarify those to make
20 sure that measurement of the perfusion areas,
21 everybody had a totally perfused fibroid to enter
22 study, so all of the non-perfused --

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1 DR. NOLLER: Yes, you said that before.
2 You said that in the 10 minutes.

3 DR. TEMPANY: Okay. Sorry. And just to
4 concur with what Dr. Wood was saying also, I mean, I
5 think a lot of us now believe in imaging. Certainly,
6 that size and volume are very imperfect measures of
7 any treatment effect. Certainly, in the cancer world,
8 it's not being regarded any more as really being the
9 most accurate measure of effective drugs, and this is
10 where I think we're going to learn a lot more. And
11 somebody asked about FMRI and perfusion imaging, and
12 these are certainly neutrals that we're definitely
13 going to apply. They're certainly not standardized
14 today, and certainly not something we could have used
15 in this trial. But to look at the consistency of the
16 fibroid, and its perfusion, those are indices that I
17 think we're going to learn an awful lot more about
18 softening and reduction in pressure in the capsule
19 which we think is probably occurring in this
20 treatment.

21 MR. NEWMAN: I'd just like to add a little
22 bit more to that. This is Rob Newman. Your question

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1 about was the reader blinded. The treatment effect is
2 very obvious, and it would be -- you see a very large
3 -- there's just an example from an image we showed you
4 before. When you get a very large non-perfused volume
5 in the middle of a well-perfused fibroid, it's going
6 to be very easy to tell without any dates on the image
7 to tell which is the pre-treatment and which is the
8 post-treatment images.

9 DR. NOLLER: Other panel discussion
10 regarding question 2.

11 DR. MILLER: It would have been very
12 worthwhile to have the data stratified regarding the
13 location of the fibroids. I mean, even if we
14 acknowledge that size may or may not have a
15 significance, I think there's reason to believe that
16 location does affect at least the symptom severity
17 scale, assuming that most of it represents menstrual
18 bleeding aberration, and some of it represents
19 pressure aberration; that indeed those myomata that
20 were deeper set or impact the cavity, or in fact may
21 be within a cavity in part, may or may not relate to
22 the reduction of your scale. Do you have any

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1 information about that?

2 DR. STEWART: This is Elizabeth Stewart.
3 We do have some information about location influencing
4 symptoms. That was one of the things we looked at in
5 our logistic regression model, and we found that
6 fibroid location did not effect outcome.

7 With regards to the question about whether
8 we primarily got improvement in bleeding symptoms or
9 bulk symptoms, that the way that the symptom severity
10 score is designed, it actually has questions that
11 cover bulk. It isn't separately validated to be able
12 to say we improved on bleeding versus we improved on
13 bulk. However, we did look at the data because some
14 of the questions clearly relate to more bleeding-
15 related questions, and some related to bulk. And
16 there didn't seem to be a difference. We got benefit
17 in both.

18 DR. NOLLER: Yes, Dr. Roberts.

19 DR. ROBERTS: One of the questions that I
20 had that was not clear to me from this was oftentimes
21 it seems as if, if you have a, for example, a
22 submucosal fibroid and you've got someone with

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1 bleeding, it's probably that submucosal fibroid that's
2 causing it. Even if they've got other fibroids that
3 are subserosal, they're not causing the bleeding.
4 It's the submucosal one that is. My question is, if
5 you had someone, let's say, that was bleeding, and had
6 multiple fibroids, could you target the fibroid that
7 you felt was causing the symptoms, whether it was bulk
8 symptoms or whether it was bleeding symptoms?

9 DR. STEWART: Absolutely.

10 DR. ROBERTS: You could.

11 DR. STEWART: Absolutely, and in fact --

12 DR. ROBERTS: And you're saying that it
13 didn't make any difference, you could treat the one
14 that you would say was probably causing the symptoms,
15 and it didn't make any difference, didn't help at all?

16 DR. STEWART: No. What I'm saying is that
17 we saw patients who had benefits in bleeding, and we
18 had patients who had benefit in bulk symptoms. But we
19 did absolutely tailor the treatment to the patient
20 symptomatology.

21 Now clearly in some patients where there's
22 only a single fibroid, there's no decision making to

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1 be done. It's intuitively obvious if there's one
2 fibroid and you treat it. However, the second level
3 of assessment in terms of determining which fibroid to
4 treat in women that have multiple fibroids, is are
5 there any that are unsafe to treat. And so going back
6 to the issues about is it too close to the spine, does
7 it meet our treatment parameters? We have to assess
8 that. But barring an exclusion for that, then we did
9 have the patient symptomatology at baseline and could
10 then choose to have -- for example, if the patient had
11 bladder frequency, and she had one fibroid that was
12 clearly in the lower uterine segment, and another that
13 was up on the fundus and fairly subserosal, we could
14 choose to treat the one nearest the bladder as a
15 primary goal. And so we did tailor our treatment to
16 the patients presenting symptomatology.

17 DR. NOLLER: Thank you, Dr. Stewart.

18 DR. ROBERTS: Can I just --

19 DR. NOLLER: Yes.

20 DR. ROBERTS: Just a follow-up. And were
21 you successful in all of these patients in treating
22 the fibroid that you felt was the most likely one to

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1 cause their symptoms, or were there patients where the
2 fibroid that you would have wanted to treat, you
3 couldn't treat because of its positioning?

4 DR. STEWART: I don't believe there were
5 any cases where we couldn't. I can defer this to
6 Clare. I think in almost all cases we were able to
7 target the primary fibroid that we thought was
8 symptomatically most important. And in some cases, we
9 were able to target more than one in terms of the
10 limitations that we sometimes went into treatment
11 saying we'd like ideally to treat two fibroids. And
12 in some of those cases, we could treat two, and in
13 others we could only treat one. And I don't know
14 whether you would like to amplify.

15 DR. TEMPANY: Yes. This is Clare Tempany
16 again. No, I mean, absolutely. It's very rare that
17 we weren't able to treat a fibroid that we had
18 identified on baseline imaging. This one case that I
19 remember that the bowel literally had fallen all the
20 way down between the fibroids and the anterior
21 abdominal wall so we didn't treat her, but very rare.

22 DR. NOLLER: Dr. Weeks.

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