

1 DR. WEEKS: Jonathan Weeks. In your
2 evaluable patients in the pivotal study, as I recall,
3 you had 20 some patients that went on to receive other
4 treatment, hysterectomy or other treatments. I think
5 perhaps there was a link there that ties into what Dr.
6 Diamond was getting at. If many of these patients had
7 multiple fibroids, and over the course of six months
8 or a year you may have effectively treated one or two
9 of the fibroids, but one would expect that there would
10 be growth in some of the other fibroids. I think it
11 would interesting to look at those images and get
12 volume information on the entire uterus for that
13 reason.

14 And I also wondered if you got
15 pathological information from those treatment failures
16 so that you could look at the extent of thermal injury
17 and the original fibroid sizes.

18 DR. STEWART: Ebbie Stewart again. We
19 have obtained tissue in as many cases as we can from
20 patients who underwent surgery, and we have at the
21 minimum gotten operative notes and pathology reports
22 on everybody that has gone on to have additional

1 surgery.

2 We haven't been able to find any evidence
3 that there was more extensive thermal damage than was
4 recorded at the time of the treatment, and there was
5 no case where there were found to be significant
6 pelvic adhesions or injury that suggested that there
7 was damage to the serosal surface. And clearly, we
8 want to take those specimens and study them further
9 from here on out.

10 I think also the fact that women went on
11 to a different treatment, we have classified them as
12 failures, and I think that's the right thing to do for
13 them. But many of them actually did have some
14 significant decrease in their symptoms from treatment,
15 but then when they had a recurrence of their symptoms
16 felt that they wanted to go on to more definitive
17 treatment.

18 I think the constraints that we had in
19 this protocol really maximized safety, to make certain
20 that we didn't get to the serosal surface, the
21 endometrial surface. We didn't ablate large volumes
22 of tissue, but I think that did limit our efficacy.

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1 And as we move forward, I think to get maintenance and
2 longstanding relief, we may either need to be more
3 aggressive in our treatment, or to choose different
4 treatment candidates. I think that the efficacy that
5 we saw was very impressive given the constraints that
6 we worked under for the protocol.

7 DR. NOLLER: Thank you. I want to remind
8 the panel that this isn't a question and answer
9 between the sponsor and us. We are discussing among
10 ourselves. There just happen to be 60 people out
11 there that are listening in on our private discussion
12 here, so let's try to discuss and help each other out
13 with answers. For example, as we had going there, and
14 then we'll turn to the sponsor if there are things we
15 really don't know that we need to know, but let's try
16 to discuss some of these among ourselves.

17 Were there other things about Question 2
18 that you want to discuss before we move on to the next
19 one?

20 DR. BRILL: Well, I would just like to add
21 that just as Dr. Stewart has said, that our ability to
22 evaluate these patients is relatively primitive

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1 because of our lack of instruments. I think we're
2 even more primitive in our ability to explain why
3 women do or do not bleed with uterine fibroids, and
4 even beyond that, it's incredibly presumptuous to
5 assume that a patient with abnormal bleeding and
6 fibroids necessarily is bleeding from those fibroids,
7 and doesn't have a coincident coagulopathy, and
8 doesn't have some sort of coincident dysfunction at
9 the endometrial level which we haven't been able to
10 identify.

11 With that said, what I'm hearing in part
12 is when you have a technique that is a selective
13 myomectomy technique, and unto that I think there's
14 some presumption, because clearly I do not wish
15 fibroid to selectively destroy having multiple
16 fibroids. We do know from the uterine artery
17 embolization data that the response in the context of
18 diminished abnormal uterine bleeding is not
19 necessarily related to the location of the myoma
20 whatsoever, so I think that we're all sort of treading
21 water here, and walking on thin ice when it comes to
22 really knowing what we are or aren't doing, and

1 deciding in a defining way which fibroid we're going
2 to treat.

3 DR. NOLLER: Yes.

4 DR. ASCHER: I have, maybe it's a naive
5 question and I apologize. Does not knowing the
6 ultimate durability really change whether something is
7 effective even in the short term? And maybe someone
8 in the panel or elsewhere can address it. I'm trying
9 to get a handle on effectiveness.

10 DR. NOLLER: Things can be effective for
11 an hour, a day, a week, a month, a year, for life.

12 DR. ASCHER: Okay. That will certainly
13 impact on some of the discussion.

14 DR. NOLLER: I don't think we are going to
15 consider approving something that works for an hour or
16 a day, but 10 days - where does it end?

17 DR. ASCHER: Something like GnRH analog as
18 a temporizing method. I mean, there is some precedent
19 for temporizing.

20 DR. NOLLER: Particularly in the peri-
21 menopausal. Did you have a comment, Dr. Wood?

22 DR. WOOD: I was just going to reiterate

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1 what I said before, that I think the imaging out
2 parameters as a surrogate marker of efficacy are
3 unreliable, and we should rely on them more for safety
4 issues here. And the bottom line is we don't have a
5 perfect questionnaire mechanism, quality of life
6 mechanism, but they used the best one that's out
7 there.

8 DR. NOLLER: Other comments before we move
9 on?

10 DR. BROWN: So my answer to 2 would be
11 that the volume does not seem to contribute at all,
12 because it doesn't seem -- to me, the volume changes
13 were not impressive. And secondly, we don't know that
14 that means anything, but there were consistent changes
15 in the questionnaire that although the amount of
16 effect was not as great at 12 months, there still was
17 some persistent effect.

18 DR. WOOD: As an aside, the time course
19 and volume changes are similar to palliative thermal
20 ablation with needle-based techniques for soft tissue
21 tumors and cancer, and the periation can happen.
22 Again, maybe if -- I don't know the mechanism, nobody

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1 does, maybe decreased interstitial pressures within
2 the tumor can have an effect without actually getting
3 rid of the whole cancer, just as an aside again.

4 DR. NOLLER: Should we move on to the
5 third question? Here I think we will need the sponsor
6 to respond to some of the physics questions we asked
7 before. The third question is, has the sponsor
8 demonstrated the MR thermal mapping provides adequate
9 intraoperative feedback during the treatment regimen,
10 sufficient to ensure safe and reliable dosing to the
11 intended fibroid tissue? Drs. Diamond and Roberts,
12 any comments about that?

13 DR. MILLER: Dr. Noller, where are you
14 reading these questions?

15 DR. NOLLER: It's in your packet. The
16 left-hand pocket. You may have received a previous
17 version. It's a couple of weeks old. It looks like
18 this. Okay. Yes, Dr. Crum.

19 DR. CRUM: This follows up some of my
20 earlier statements, and I'd sort of like to make a
21 comment because we're sort of discussing this amongst
22 ourselves rather than asking the sponsor and so forth.

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1 DR. NOLLER: But we will ask them.

2 DR. CRUM: So it seems to me that the
3 monitor, MR temperature monitor assumes that you get
4 a temperature elevation. It's not an absolute
5 measure, it's temperature elevation. And it also
6 makes the assumption that after the treatment, we
7 start in a sense de novo again at exactly the same
8 temperature that you started last time; that is, at
9 37. And when you destroy the vascularity of that
10 region, you also shut down the perfusion. And so the
11 perfusion is not a major factor in carrying the heat
12 away, but nonetheless, if it's adjacent to a treated
13 region, the heat has to go somewhere. So to assume
14 that you're going to come back to the initial
15 conditions ab initio in each case, I think is a
16 questionable assumption.

17 The temperature increase that does occur
18 in this model assumes some very simplistic conditions,
19 no non-linearity, no temperature dependent
20 attenuation, so forth and so on, so it's not
21 surprising to me that the prediction of the thermal
22 dose differs from the non-perfused volume. This is

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1 complicated stuff. I mean, doing modeling inside
2 biological tissue and these sorts of conditions are
3 difficult to do.

4 But the endpoint of this is that after you
5 do this treatment, you can go back in and get a non-
6 perfused volume that's correlated pretty closely; that
7 is a factor of like 2 or some number different from
8 the computed thermal dose. So even though there might
9 not be a one-to-one prediction, there is a
10 correlation. And similarly, empirically one can get
11 the non-perfused volume, which I think is certainly
12 what induces the biological effect and the successful
13 treatment, so I think that there are some
14 inefficiencies and inaccuracies perhaps in the thermal
15 model, but to answer the question, does this provide
16 a reliable doing, with some modification, yes. I
17 think that that's true, and I would invite you to
18 comment on it.

19 DR. NOLLER: Dr. Diamond.

20 DR. DIAMOND: I have a question. Do you
21 understand from the way the machine works whether a
22 second sonication would be adjacent to the first one,

1 or would it be some place far distant, because if it's
2 next to it, you're going to have a potentially greater
3 thermal effect than if it's at a big distance on the
4 other side of the fibroid.

5 DR. CRUM: I don't know how they do that.
6 I know that in other situations involving HIFU
7 applications, focused ultrasound, people tend to go
8 here, then there, and then back and forth, rather than
9 do the adjacent one, so it's a question now for the
10 sponsor to answer; do you do adjacent ones, or do you
11 do --

12 DR. NOLLER: Let's hold up just -- did you
13 have something to say, Dr. Wood, and then we'll go to
14 the sponsor.

15 DR. WOOD: I was just going to say there's
16 a spiral mechanism out there, as well, which takes
17 advantage of that very effect and changes the modeling
18 completely, and the effect. And one more question -
19 maybe you guys could answer while we're here -
20 adjusting the calibration in the beginning offset the
21 test zone. That test zone, is it just done once? And
22 if not, do we have any information on how tissue

1 tissue-to-tissue interfaces in interactions between
2 your transducer and the fibroid can affect future
3 inhomogeneities in your treatment zone? And would it
4 be more effective to have more than one test zone
5 done?

6 DR. NOLLER: Would you address those
7 questions, please?

8 DR. TEMPANY: Yes, I'd be happy to. This
9 is Clare Tempany again. To answer your question about
10 how we do the sonications, you can do it either way.
11 You can either go one, two, three, four, five and
12 across. More commonly, we will go from one part to
13 the other. There is a time penalty with that because
14 you're moving the transducer. But certainly, we
15 receive the return to temperature baseline on the
16 graph, so you'll see it return to baseline
17 temperature. If it doesn't return to baseline
18 temperature in the 90 seconds, clearly the easy thing
19 to do is to move to a completely different location
20 and go to the opposite side of the fibroid, and then
21 take that even two or three sonications later before
22 you get back there.

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1 And yes, we're continually verifying the
2 location of the sonication because you have the
3 coordinates. So even if there is beam attenuation,
4 you will see whether it's off, and everything is
5 registered both in short axis and long axis. We can
6 choose to do it in sagittal or coronal plane. Does
7 that answer?

8 DR. NOLLER: Thank you. Other discussion
9 on this topic?

10 DR. BRILL: I'd like to just to ask the
11 technical expertise of the panel, is there any concern
12 that there's monitoring of the differential between
13 core temperature and realized temperature versus
14 absolute instantaneous temperature monitoring as it
15 was presented this morning? I believe it was stated
16 that it was a differential between core temperature,
17 was it not?

18 DR. NOLLER: Dr. Crum.

19 DR. CRUM: I think the question was
20 appropriately answered. If you have a monitor that it
21 drops back down to the background, they want it to
22 drop back to the initial condition. And I presume

1 that the initial condition was 37, so if it drops back
2 to that initial condition and they do not fire the
3 second shot until you've dropped back to the initial
4 condition, that you're back ab initio again, you're
5 back where you started. So I don't see that the core
6 temperature is going to come up very much, maybe 1
7 degree or so, but I don't see that being a problem
8 myself.

9 DR. DIAMOND: I'd like to ask also again,
10 the FDA presentation, they had two physics
11 presentations, each of which seemed to be suggesting
12 that there are lots of potential where measurements
13 and assumptions could lead to big temperature
14 elevations greater than might have been expected and
15 leading to tissue injury, but yet both ended up
16 concluding that the likelihood of injury was actually
17 rare, and having given us that presentation. What is
18 your interpretation of that from what was presented?
19 Is that going to be an exceedingly rare occurrence, or
20 are the scenarios that we're describing as potential
21 concerns, are they things that are perhaps more
22 frequent?

1 DR. CRUM: I mean, I have lots of
2 concerns, but for example, there was no treatment of
3 what happens if there is bowel gas. I didn't hear a
4 discussion of that. I'm sure they have thought about
5 that, but if you have bowel gas, then you have other
6 effects that are non-thermal, cavitation. And the
7 literature is full of descriptions if you have bowel
8 gas and you have either Lithotripter or other kinds of
9 even diagnostic ultrasound pulses, you can get damage
10 to the tissue in the bowel from the result that you're
11 trying to drive a pressure release interface. That
12 was not discussed. Maybe the sponsors could discuss
13 that.

14 The other thing is that non-linear effects
15 and changes in the various tissue layers, as Dr. Wood
16 was mentioning, will cause focusing in different
17 regions that you would anticipate. And, of course,
18 they argue that they do the sublethal measurement each
19 time, and then they correct. If they do that every
20 time, then that corrects for that error. And so I
21 think that the FDA's analysis is that there is some
22 areas that should be watched, and I presume that those

1 directions will be given to the sponsor, and they will
2 address those.

3 MR. WEEKS: This is a question, and I have
4 no idea what the answer is; but the coupling gel
5 itself, is there any reason to believe that there can
6 be a variation in say that quality assurance and the
7 density of that material, and as it's mass produced or
8 whatever, can there be enough variation that that
9 changes the thermal injury or damage in any way?

10 DR. CRUM: What happens with that is that
11 -- and I think that's been addressed also, is if it's
12 not adequately coupled to the patient, and if you move
13 around and you introduce a bubble or a void of some
14 sort, then you have a potential problem because then
15 you're going to get a skin burn or something.

16 MR. WEEKS: I'm concerned with like the
17 density or say the density of the material itself, so
18 assuming it's got good skin contact --

19 DR. CRUM: It's typically acoustically
20 transparent, so there's very little attenuation in
21 that material, and so there should be no effect on
22 that material from the ultrasound because it's

1 essentially acoustically transparent. When we have an
2 interface with gas, then you can have a problem, but
3 not if you have adequate coupling.

4 DR. NOLLER: Dr. Samulski, did you have --

5 DR. SAMULSKI: I agree with this off-the
6 shelf kind of interface that you use when you use
7 ultrasound in a clinic for diagnostics, and this
8 application as well. I think the sponsors must have
9 tons of data testing animals and stuff like that, and
10 could give you an idea of what the outcome was.

11 DR. NOLLER: Why don't we stop at this
12 point and see if the sponsors have any comments
13 regarding this discussion that's been going on for a
14 few minutes.

15 DR. VORTMAN: Kobi Vortman, employee from
16 InSightec, paid by InSightec. I'll try to address
17 first the cavitation. Cavitation was a major issue in
18 the design of the system. We had a real time
19 integrated detector that continuously during the
20 sonication is receiving the signal and looking for any
21 clue for cavitation, which right now is between half
22 of the frequency and then several minutes. In our

1 training or in our instructions for use, the spectrum
2 appears. You can see it here.

3 On the left side you see a different
4 spectrum without the cavitation. Okay. And on the
5 right side here, you could see what happens when the
6 detector detects cavitation. You'll see a wide
7 spectrum white noise, and the user is instructed to
8 immediately switch off the system in this case, and
9 move to some other place.

10 And as Dr. Crum said before, cavitation
11 pressure could change as a result of temperature and
12 so on, so this is a major tool. I would add to this
13 that in addition to the cavitation at that point, we
14 have a reflection detection continuously. So if the
15 signal received by the system is detecting any air
16 bubble or air surface, the system will detect it, and
17 again the user is instructed to switch off. Okay. So
18 that's, I believe, in response to -- here you could
19 see the reflection detector. And what we do, in
20 addition to measuring reflection, we are measuring it
21 on the scale, AP coordinate, so you will be able to
22 allocate it to the area which generated the

1 reflection. So if it be internally, the bandwidth
2 would be 76 or 102. At the interface between the
3 transducer and the skin line, it would be 50, so you
4 would be able to allocate the reflection to whatever
5 place.

6 DR. CRUM: May I just ask you if that's a
7 passive cavitation detector or an active cavitation
8 detector?

9 DR. VORTMAN: It's a passive.

10 DR. CRUM: Passive, and what's the
11 bandwidth?

12 DR. VORTMAN: The bandwidth is between 20
13 kilohertz and about three and a half megahertz, while
14 we're working at 1.1.

15 DR. CRUM: So you're just looking at the
16 subharmonic, are you not?

17 DR. VORTMAN: Correct.

18 DR. CRUM: And you realize the subharmonic
19 means stable cavitation, which means that if you had
20 this kind of intensity, you would get inertial
21 cavitation rather than stable cavitation.

22 DR. VORTMAN: Of course.

1 DR. CRUM: Why wouldn't you be looking in
2 a bandwidth up around 10 megahertz or something like
3 that?

4 DR. VORTMAN: Okay. What we have said
5 before, we are using continuously thermometry of the
6 whole field of view, so if you will have any non-
7 linear effect, like CW cavitation, we'll be able to
8 see non-linear effects through heating, and detect it
9 immediately, so we are using both. We are using both
10 passive detector and thermometry to monitor those non-
11 linear second and certain harmonic effects.

12 DR. CRUM: Do you ever think that maybe
13 the reason the thermal model is not working is that
14 you're getting submicroscopic cavitation, and that's
15 coupling through the bubbles through increased
16 heating?

17 DR. VORTMAN: This is an issue that we
18 addressed extensively. The predictor in our system,
19 both in our accumulated experience, is over-predicting
20 the dose. Okay. So we didn't see effects like this
21 at the levels that we are working. However, it could
22 have been, and as I've said, it will have something

1 like this. This should translate to either moving
2 down, shifting down the focus immediately, if the
3 focus were generating, or at some point in the way
4 overheating. So we are training our user to watch for
5 this.

6 DR. CRUM: So when you did histology, did
7 you ever see cases where you had non-cigar-shaped
8 lesion in some areas that were not treated because of
9 the non-symmetric shape of the lesion indicative of
10 some kind of inhomogenetic effect?

11 DR. VORTMAN: WE've seen it in animal
12 work. Since we've driven the system into a very high
13 intensity and we have seen in this case.

14 DR. CRUM: What about the hysterectomies?

15 DR. VORTMAN: Didn't see it there. We've
16 seen -- scoped minimum number of cavitations that were
17 switched off.

18 DR. NOLLER: While you're there, let me
19 just ask you one question. You said that the operator
20 is instructed to turn off the machine, but there's no
21 automatic shutdown, or is there?

22 DR. VORTMAN: Correct.

1 DR. NOLLER: Thank you. Okay. Yes.
2 Another point?

3 MR. NEWMAN: If I could just finish
4 answering the question too about the acoustic gel.
5 The acoustic gel, we buy it from Parker Laboratories.
6 It's a general manufacturer of it, and it's a one-time
7 use. Parker pours it for us in a specific shape. It
8 has an expiration date. We use it for a single
9 patient treatment, and then it's discarded. So we've
10 done the biocompatibility testing and all that kind of
11 stuff. Parker has done that already. And if there
12 was an issue with a problem with the density or the
13 acoustic properties of it, you'd see it through the
14 reflection monitoring when you did the testing of the
15 treatment before the patient is put on the table. We
16 set the system up and we put a phantom patient, if you
17 will, on top of a tissue specific phantom on the
18 acoustic coupling gel, and do a quick in-room check
19 before the patient is put on the table, that we would
20 detect a problem like you had suggested.

21 DR. NOLLER: Thank you. Let's move on to
22 question 4. A number of adverse effects specific to

1 ultrasound treatment occurred during the clinical
2 trial, including nerve injury, leg pain, and skin
3 injury. Question: Do the results from the thermal
4 modeling and our understanding of the underlying
5 physics provide sufficient information to understand
6 the etiology of the injuries that occurred in the
7 study?

8 I'll respond. I think the presentations
9 did a very good job of explaining how the people got
10 the injuries, I thought. It's a different question
11 whether or not there are adequate ways to prevent
12 them, but I thought the explanation made sense. Any
13 comments? Dr. Diamond.

14 DR. DIAMOND: I thought for the skin
15 injuries, that was well-explained, and I don't have
16 any questions. For the nerve injuries, some data was
17 presented to us about incidence angle and estimated
18 distance from the focus to the sacrum. Other things
19 I guess I would have liked to have seen what was what
20 known about the number of pulses, sonication pulses
21 that went to the area where the nerves were in those
22 patients. What happened to the temperature

1 thresholds, and we're shown example of how if it's a
2 little bit too high, the next sonication they lowered
3 the energy. What do we know about the patient
4 actually got injured? Did they have higher energy
5 that was transmitted?

6 DR. NOLLER: It would be particularly
7 interesting in that one page they had months to
8 resolve that.

9 DR. DIAMOND: Yes, the 9019, yes.

10 DR. NOLLER: Other questions? Yes.

11 DR. CRUM: I'd like to ask either Dr.
12 Herman or the InSightec people if you've examined the
13 side lobes, because when you show these pictures, you
14 assume a nice conical shape input for the focus wave,
15 a nice conical on the outside. What happens, of
16 course, with acoustic propagation is you get what we
17 call side lobes, which means that it doesn't follow
18 that nice conical thing. So if you had side lobes,
19 you would get hot spots outside that area. If you had
20 a hot spot on the nerve in which you didn't think you
21 were illuminating you could get some damage. So I
22 don't know whether Dr. Herman has modeled that or

1 whether InSightec people have modeled that, but I'd
2 just like to ask that question.

3 DR. NOLLER: Do you have a response?
4 Please.

5 DR. VORTMAN: Again, Kobi Vortman. Yes,
6 we have extensively modeled side lobes. The design of
7 the transducer is such that normally you don't have
8 any side lobes. The distance between elements and the
9 number of elements is such that you don't have any
10 deviation from a closely spherical surface. In
11 addition to this, we have in system tissue aberration
12 correction that is used -- I'm now probably getting
13 into too much detail but I'll say the following. We
14 are using the MR image in segmenting between muscle
15 and fat, and this could be downloaded to the bin
16 former to correct for tissue aberrations, speed of
17 sound and so on, so the bin former takes this in and
18 refocuses the focus.

19 The third point is you have real-time
20 feedback on the focal shape in any second hot spots
21 from the thermal image. So that is the reason we've
22 addressed it.

1 DR. NOLLER: What about the answer to Dr.
2 Diamond's question? I'd like both the sponsor and FDA
3 to respond to that, if possible, about particularly
4 looking at those patients that had injuries, if you
5 learned anything from those.

6 DR. ROBERTS: Could I also just ask maybe
7 a part of that, is that you've set up a 4 centimeter
8 distance. My question is did any of the patients who
9 have nerve injury, in fact, be within what you would
10 say now is within 4 centimeters, or were there ones
11 where everyone outside of that 4 centimeter area and
12 still had a problem? So I guess my question is, do we
13 really know that 4 centimeters really means anything,
14 or is that a theoretical construct?

15 DR. VORTMAN: Again, Kobi Vortman. What
16 is done, we've looked at energy intensity. The factor
17 that generates the heating is energy intensive heat,
18 and it's a multi-parametric problem. It's not only
19 what is the energy intensity, it is what are the
20 incidence angle of the beam impinging on the bone? If
21 this will be above 38 degrees, you will have no
22 heating at all. So we assumed that the combination of

1 4 centimeters that is keeping the energy intensity at
2 a reasonable level, and non-perpendicular bin would
3 build this into a safe environment, or envelope.

4 Have we seen cases in which even more than
5 4 centimeters and we had some leg pain? The answer is
6 yes. And many of those cases that I've looked at, the
7 bin was perpendicular, so you need to use both. One
8 wouldn't do the job.

9 DR. NOLLER: Did FDA have any comments
10 about that?

11 MR. HERMAN: I think we would agree with
12 that.

13 DR. NOLLER: Give your name, please.

14 MR. HERMAN: My name is Bruce Herman. We
15 would agree with that assessment with the caveat that
16 while searching for non-normality and the 4
17 centimeters are definitely steps that would markedly
18 mitigate the possibility of adverse effects to the
19 sacral nerve or something, it wouldn't -- considering
20 what I think I know about the possible variation of
21 physical structure, wouldn't absolutely rule out the
22 possibility. But again, go a long way to minimize the

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1 possibility of those effects.

2 DR. NOLLER: That helps us too with the
3 next question.

4 MR. HERMAN: It's not an absolute
5 demarcation as you mentioned, below 4 centimeters you
6 can get damage even with normality and beyond. You
7 can't. But putting both together gives, I think, a
8 broad range of physiology and tissue characteristics.
9 Looking at it with a fairly conservative eye, a
10 reasonably good possibility of having only very rare
11 occurrences of, let's say, sacral nerve damage.

12 DR. NOLLER: Thank you.

13 DR. DIAMOND: Dr. Noller.

14 DR. NOLLER: Yes.

15 DR. DIAMOND: I find both those answers
16 actually sort of unsettling, because the data that was
17 presented to us by Dr. Del Mundo, three out of the
18 five patients who actually had nerve injury had
19 incidence angles of 30 degrees or more, and distances
20 of 4 centimeters or greater. I'm uncomfortable, which
21 is why I was asking are there other parameters, such
22 as thermography or other ways that you've looked at

1 those patients where you could shed more light on that
2 information to us, and give us a greater degree of
3 comfort for the future above and beyond just these two
4 criteria.

5 DR. STEWART: Ebbie Stewart again. I
6 think the clinical input is also important here. This
7 is where the patient having conscious sedation and
8 being able to respond to discomfort, that the patients
9 who do have heating of their nerve typically do feel
10 sacral pain, buttock pain, and are able to terminate
11 the sonication. In that case, there can be
12 reassessment of the treatment plan, and moving of
13 sonication points. I think the index case where there
14 was a significant nerve injury, first of all, caused
15 us to focus in more carefully on what was going on in
16 the far field. And I think a lot of our mitigation
17 steps have brought that to bear. But I think the
18 other thing it's made us very cognizant of is the fact
19 that interacting with the patient and responding to
20 discomfort that she presents is important, as well,
21 because oftentimes when the patient is having right
22 buttock pain and you're sonicating near the right

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1 serosal surface of the fibroid, that's an indication
2 that you are potentially getting some nerve heating,
3 and that you should move before anything more happens.
4 That I think nerve injury certainly can take place at
5 the time of hysterectomy, as well. There are well
6 reported cases where the retractor or the positioning
7 caused this to bear. But we do have feedback, and now
8 we have over 600 cases where we haven't seen a
9 significant nerve energy.

10 DR. BRILL: Do you have a number of
11 instances where patients complained of heat but didn't
12 have any deficit thereafter?

13 DR. STEWART: Absolutely. And, in fact,
14 that's been one of the major things that we focused in
15 on in the continued access protocol. The study sheets
16 for the continued access protocol actually ask you are
17 there sonications where the patient has pain? And
18 then you record the sonication number, you record the
19 pain, you record the intensity of the pain, and so we
20 have been very cognizant of what's going on and
21 interacting with the patient.

22 DR. BRILL: Do you have those numbers?

1 DR. STEWART: Which numbers?

2 DR. BRILL: Do we know reported instances
3 where there were not deficits thereafter, how many?

4 DR. STEWART: Probably, Clare, maybe you
5 have a better sense than I do. I think a lot of
6 patients will report pain during sonication, that
7 certainly there is back pain from positioning, as
8 well. But most of the pain they have is fairly mild
9 to moderate, and it's pretty rare to have severe pain
10 during sonication.

11 DR. NOLLER: The question is do you have
12 numbers of patients?

13 DR. TEMPANY: No, we don't have numbers
14 but almost every patient will feel a sensation at some
15 point during the procedure related to a sonication, be
16 that something in the skin, cramping in the uterus or
17 something in their back. And that's why I constantly
18 am asking them before we hit the sonication button
19 telling her we're about to do one, and then afterwards
20 how do you feel about that? And then if there's any
21 sensation I move to a different place like I just
22 described, to the other side of the fibroid to allow

1 that area to completely cool down, and then try to
2 come back again. This is constant feedback.

3 DR. NOLLER: Dr. Roberts.

4 DR. ROBERTS: I'm a little bit confused
5 though because you say that all of these patients have
6 positional pain, whatever. Is there something very
7 specific about this complaint of pain that makes you
8 feel that this is going to be a nerve problem? I
9 mean, is there something that the patient describes
10 that you then say uh-oh, I better move to some place
11 else? Or do you just say well -- what I'm thinking
12 about is I'm trying to think ahead. Okay. Now you're
13 going to have instructions for use, and how are you
14 going to explain to your users and to the patient, you
15 need to tell me when you feel like this, because that
16 means I need to move what I'm doing, as opposed to
17 well, my back is getting sore and so you give her some
18 more drugs.

19 DR. TEMPANY: Oh, absolutely. I mean, we
20 give her guidelines ahead of time, and I explain the
21 sensations that I expect potentially during a
22 sonication, ranging all the way through from near

1 field to far field. And when it's related to nerve
2 stimulation, they are going to feel an electric
3 sensation going down their back.

4 DR. ROBERTS: Okay. So it's a specific
5 type of feeling that they're going to have.

6 DR. TEMPANY: Yes.

7 DR. ROBERTS: It's not with a dull ache in
8 their back. It's going to be electric shock.

9 DR. TEMPANY: Yes. And it's absolutely
10 temporally related to the sonication.

11 DR. ROBERTS: Okay.

12 DR. TEMPANY: Where if it's positional,
13 it's going to be there no matter what we're doing.

14 DR. NOLLER: Dr. Crum.

15 DR. CRUM: Larry Crum. I just wanted to
16 point out in some unpublished data, there is a company
17 in the Seattle area that's doing catheter wound
18 sealing with ultrasound HIFU. And, of course, near
19 the femoral artery there are several nerves, and they
20 actually use this as an indication of when they're
21 targeted. They say do you feel the pain, and when
22 they do, then they move. So nerves are very sensitive

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1 to this rapid thermal increase.

2 DR. TEMPANY: Yes. And the patients can
3 give you instant feedback.

4 DR. BRILL: Is there anyone on the panel
5 who at least can help me understand whether the pain
6 is coming from a thermally perceived event on nerve?
7 Is it something that's physical? And if it's thermal,
8 then how good is our modeling for temperature change
9 during this process? I guess I'm still confused.

10 DR. NOLLER: Dr. Wood.

11 DR. WOOD: Brad Wood. I think the modelers
12 are confused as well as the physiologists because we
13 don't know. I think the assumption is that nerves are
14 more sensitive in normal tissue to damage, and there's
15 a spectrum of damage. And we're seeing that in some
16 of these adverse events.

17 There's actually -- you can do thermal
18 neurolysis where we target the nerve with a certain
19 temperature and burn the nerve on purpose for
20 therapeutic pain relief, and there's a method there
21 for pulsed radio frequency where we use a 42 degree
22 level, and apply milliseconds of pulsed energy through

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1 a needle, measure the temperature at the spot where
2 we're delivering, and 42 degrees is therapeutic there.
3 The pain fibers are more sensitive in a nerve than
4 normal fibers to heat effects, and there may be some
5 other effects going on there that may change the
6 conduction specific to that frequency, which is
7 different than this. But there's a number of issues
8 here that are complex, and I think looking at the
9 thermal modeling of the nerve damage, for example, you
10 know, the number of assumptions there. I think we're
11 kind of dancing around the issue.

12 I don't think we have a true handle. I
13 mean, certainly mitigating steps are helping to
14 decrease the risk and have helped, but I don't think
15 we have a true handle of the -- from a scientific
16 point of view what is actually going on in there when
17 it's dependent on conduction from bone back to the
18 sacral nerve, and that conduction is affected by
19 convective heat loss of nearby vessels, and the
20 properties of the tissue nearby, and those tissue
21 properties change as the heat goes up, so I think it's
22 all -- I don't think we know really from a modeling

1 point of view, or scientific point of view, except
2 that the nerves are more sensitive.

3 Another issue that comes up when we treat
4 therapeutically, not neurolysis, or not treating
5 nerves for pain. In this case again, treating cancer
6 near nerves for pain. Treating cancer near nerves for
7 pain in order to get rid of the cancer with thermal
8 ablation needle-based, we will do it with conscious
9 sedation. We'll keep that sedation very light during
10 the whole procedure, and there is a typical -- we'll
11 train the patient beforehand extensively. If you feel
12 this symptom related to whatever nerves were near, and
13 we know what those nerves are going to feel like
14 depending on the innervation, if you know that symptom
15 and if that develops, let us know right away. And we
16 keep them light, and it's a painful procedure for the
17 patient because we don't give them the sedation that
18 they need. It's a conscious sedation. It's not a
19 deep sedation, so it's a very challenging thing, and
20 I would ask you all how are you going to ensure that
21 users and physicians are going to be able to titrate
22 this fine balance between sedation and feedback, which

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1 is imminently related to the safety for nerve damage.
2 It's a hard thing to do. Is there any level of
3 consciousness issues?

4 DR. NOLLER: Can I ask you to hold? Let's
5 do that as part of the next one, because I think
6 that's an important question, but I think it fits
7 better with Question 5, than Question 4.

8 DR. MILLER: Can I ask something about
9 Question 4? I'm just wondering from our panel if
10 there's any sense that the extent of nerve injury is
11 understood in the brief proximity of follow-up. In
12 other words, is there any reason to believe
13 physiologically that there might be nerve injury that
14 hasn't been perceived yet, because it's going to take
15 longer.

16 DR. NOLLER: Three years, four years, five
17 years.

18 DR. MILLER: Right. Clearly, these nerves
19 are getting energy of one kind of another.

20 DR. NOLLER: Anybody on the panel a
21 neurologist?

22 DR. ROBERTS: My personal feeling is that

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1 if you get nerve injury, you're going to find it out
2 quickly. Unless you have a lot of scarring or
3 something in the area that later on develops some kind
4 of nerve problem - I mean, I suppose that's possible -
5 but I suspect that with this kind of things it's going
6 to be presumably a thermal injury, and it's going to
7 occur at the time that -- or right around the time
8 that you start this whole process, or do this whole
9 process.

10 DR. NOLLER: Dr. Crum.

11 DR. CRUM: I have a Ph.D. student who's
12 trying to develop a HIFU system to treat chronic pain,
13 and so what we've done is done various levels of
14 intensity and looked at the histology of the damage to
15 the nerve system on animal models. It's a pretty
16 complicated thing. We don't understand it yet, but I
17 think this follows Dr. Wood's comment. I don't think
18 you're going to find out in a human, and it's a very
19 complicated thing even in an animal model, so I don't
20 have anything to add other than it is much more
21 sensitive. The nerve is more sensitive to the thermal
22 effect than other tissue. And there are various

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1 degrees of damage. You can damage the myelin sheath,
2 for example, and cut down some pain. But again, that
3 doesn't totally disrupt the axon conduction.

4 DR. NOLLER: Dr. Wood.

5 DR. WOOD: I agree totally, but I can't
6 imagine seeing any subacute or chronic effects from
7 thermal induced damage to a nerve. You get what you
8 get, and you're not going to see anything down the
9 road. I think the six to twelve month follow-up we
10 have here is perfectly adequate to assess those
11 issues.

12 DR. NOLLER: Let's move on to Question 5.
13 And for this the chart that's attached is important.
14 Adverse effects, noted potential risks related to the
15 use of the device prompted the development of active
16 mitigations as identified in the attached chart. Are
17 these mitigations sufficient to ensure safe use of the
18 device? Given the effectiveness achieved, do the
19 benefits outweigh the risk for this device? Let's
20 discuss this a bit, and then we'll ask the sponsor to
21 also discuss it.

22 DR. BRILL: I think it was alluded to this

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1 morning. At least for me, I'm still confused as to
2 how the 15 millimeter, 5 millimeter, 33 percent
3 formula was established. My sense was that it was to
4 minimize the chance that there would be a thermal
5 margin that would affect something vital.

6 DR. NOLLER: And some of that has been
7 changed now in the continued access protocol.

8 DR. BRILL: So I guess I need to
9 understand some objective explanation that
10 substantiates these parameters.

11 DR. NOLLER: FDA, were those distances
12 chosen based on literature and sort of a best guess?
13 Okay. The distances that were in the original
14 protocol, 15 millimeters from serosa and endometrium,
15 30 percent volume. Were those based on best guess of
16 safety? This should be safe. Was that the idea
17 behind those numbers?

18 DR. DEL MUNDO: Basically, it boils down
19 to a check on what we felt to be safe from the pre-
20 hysterectomy studies. As Dr. Corrado had mentioned,
21 there was one occasion where an area of what appeared
22 to be an area affected by sonication outside the

1 capsule of the fibroid was noted, and that along with
2 increased volume that we saw that was greater than the
3 treatment, those all factored into our decision and
4 the company's decision for those particular margins
5 and volumes.

6 DR. NOLLER: Thank you. Yes.

7 DR. ASCHER: What was the thinking to
8 disregard any concern about the endometrial
9 requirement was dropped for the continued access
10 study? Did they do hysteroscopic looks? Was there any
11 incidence of adhesions caused if you had a sonication
12 that crossed the endometrial canal and just a little
13 -- I don't understand why that was --

14 DR. NOLLER: I was wondering the same
15 thing. You knew what I was thinking. My thinking was
16 kind of who cares, but maybe there's more to it than
17 that.

18 DR. ASCHER: You know, I can see that
19 these women maybe aren't going to get pregnant because
20 that was a contraindication, but if you caused a
21 significant adhesion if they're peri-menopausal and
22 still having menses, an adhesion could be --

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1 DR. NOLLER: To the endometria or --

2 DR. ASCHER: Yes. So I didn't know, did
3 anybody look hysteroscopically and see that there was
4 no problem, or if crossing the endometrium had no
5 clinical sequelae?

6 DR. NOLLER: Dr. Crum.

7 DR. CRUM: I don't want to address that
8 issue. I want to talk about another issue, so if you
9 want to follow-up on her comment.

10 DR. NOLLER: Any more thoughts about that?
11 Dr. Stewart.

12 DR. STEWART: Ebbie Stewart. We haven't
13 seen any endometrial damage throughout the protocol.
14 We haven't had any patients who underwent procedures
15 who were documented to have adhesions. We also
16 haven't seen what has been seen with some uterine
17 artery embolization patients, and that's the fibroid
18 being expelled vaginally, so I think maybe -- I can't
19 speak for the FDA on why that was an original
20 constraint, but we certainly haven't seen any
21 endometrial problems. Now certainly, our patients
22 were chosen because they weren't interested in future

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1 fertility, so there could be some issues there for the
2 future.

3 DR. NOLLER: Dr. Crum.

4 DR. CRUM: This enhanced volume effect, I
5 think is very important, so there's two hypotheses
6 that sort of contribute to how cysts form or its
7 consequence. One is that it's ischemic, and that
8 makes a lot of sense. That sort of effect shows up in
9 Lithotripsy a lot, and I think that's probably right.
10 If that's true, then because the fibroid, as I
11 understand it, usually comes from a central blood
12 supply, so if you have enhanced volume effect, you
13 probably would only damage the fibroid, and you
14 wouldn't go somewhere else if it's basically coming
15 from that central blood supply.

16 On the other hand, I'm not really
17 impressed with some of your thermal modeling, and it
18 could be it's a thermal modeling effect, and that
19 you're not correctly addressing the thermal modeling.
20 That is to say that the volume that you calculate in
21 terms of thermal dose is much less than what you
22 actually get, and if that's true, now you do have to

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1 worry about damage to the endometrium and other areas.

2 DR. STEWART: Ebbie Stewart again.

3 Certainly, there is a possibility that the extension
4 of treatment is via an ischemic effect. Certainly, in
5 the pathology that we examined, we tended to see more
6 coagulative necrosis, rather than ischemic necrosis.
7 But we also had a relatively limited number of samples
8 and a short sampling interval.

9 There is also another explanation from the
10 fibroid literature, and that comes from some
11 experiments where in trying to assess the feasibility
12 of gene therapy for fibroids, Greg Christman at the
13 University of Michigan has shown that you get a
14 substantial bystander effect, that if you kill one
15 cell, you get substantially more cells that are
16 killed. And his hypothesis is because gap junctions
17 are frequent in fibroids, that if you generate tissue
18 death, then apoptotic mediators may be able to be
19 spread through the fibroid. And so I think everything
20 that we've seen does suggest that the extension of
21 damage is to the treated fibroid. The one case where
22 there was damage at the serosal surface was incorrect

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1 targeting and was not an extension of the injury
2 passed that border.

3 DR. CRUM: Just follow that up, can I
4 follow that up with a question? Larry Crum. Forgive
5 this comment, but I mean, if it's ischemic, why don't
6 you just go in and treat the major vessel supplying
7 your fibroid?

8 DR. STEWART: That's one --

9 DR. CRUM: You can see it with ultrasound,
10 you know.

11 DR. STEWART: Yes, that's one strategy we
12 have contemplated for the future. I think the vessels
13 don't really come from the center of the fibroid, they
14 come from the periphery, so that gets to our margin
15 errors. But one of the things we would like to do in
16 the future is to be able to compare interstitial
17 treatment to peripheral treatment to kind of address
18 that question.

19 DR. NOLLER: Let's focus a bit on these
20 mitigations. That's what the question is about. We
21 have four risks in the table, and the mitigation in
22 the pivotal study, and then the continued access

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1 study. Are there things there that people are
2 uncomfortable about? We've already talked about the
3 unintended heating of bone and nerve for some length,
4 the skin burns. It appeared to me that with careful
5 attention to the skin, they've been able to mitigate
6 that problem. Adjacent anatomy we were just talking
7 about a bit. Other comments about any of those four?

8 DR. BRILL: Well, just for my own
9 clarification, on one hand there's 4 centimeters
10 between treatment focus and the sacral nerves, which
11 I believe is a function of heat transfer, and that
12 would be the issue. Now we have a minimum of 15
13 millimeters to the outside of the uterus, which has
14 bowel on the surface. Now we've kind of visited this
15 issue on a previous panel before, and is there any
16 cause for concern that on one hand we're seeing the 40
17 millimeters between the maximum temperature and the
18 sacral nerves, and yet we turn it down to 15 for maybe
19 a piece of bowel that's on the surface of the uterus.

20 DR. NOLLER: Any comments?

21 DR. WOOD: Speaking from other thermal
22 techniques, 15 is plenty. We can -- with care and

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1 experience, you can get very close to bowel, a little
2 risky, obviously, but you can get closer than 15
3 millimeters and a liver with bowel touching it.
4 Perfused organ, different issues, more prone to
5 convective heat loss, but not as sharp of a margin as
6 focused ultrasound between heated and unheated. So
7 assuming no secondary side lobing or tissue-tissue
8 secondary burns, which it sounds like they are not,
9 it's probably adequate.

10 DR. MILLER: My question relative to the
11 unintended heating of adjacent anatomy has to do with
12 the patient movement. I mean, I know that the patient
13 is situated and they're sedated, but they're also in
14 that tube for a while, and there's lots of
15 sonications. If they have an itch or they get a
16 scratch while they're being sonicated, aren't you
17 going to be heating unintended tissue?

18 DR. TEMPANY: Certainly, we don't want the
19 patient to move. We have a nurse who hopefully can
20 scratch their nose for them. But seriously, we can
21 see motion. And certainly in the feasibility trial
22 where we didn't empty the bladder, we did see motion.

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1 And when you see significant motion, a millimeter or
2 two, you stop the treatment, and you actually replan
3 all over again, so that's what we actually did several
4 times I can tell you, much to my frustration at times
5 because it was restarting all over again. You replan
6 and you draw the circles again, and then you replot
7 your sonication so if there's significant you can
8 definitely do that.

9 DR. WOOD: Another sort of side point -
10 Brad Wood. The fiducials, is there a least common --
11 is it dummed up enough so that the end user has to
12 use fiducials? And if so, do they have to use a
13 number of them, not just one?

14 DR. TEMPANY: Yes, remember the drawing --

15 DR. WOOD: But that's a requisite.

16 DR. TEMPANY: Yes. That's a step in the
17 prep process.

18 DR. NOLLER: Dr. Hayes.

19 DR. HAYES: I was wondering, is the nurse
20 the one that monitoring this conscious sedation such
21 that they will be able to tell you of discomfort, but
22 yet be quiet enough? Who's monitoring the conscious

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1 sedation?

2 DR. TEMPANY: Myself and the nurse, the
3 doctor performing the procedure and the nurse. The
4 nurse is actually in the room right beside the
5 patient, so she's closer and can maybe hear her
6 slightly better sometimes. But between both of us,
7 we're both -- we have monitors as far as the pulse,
8 blood pressure both inside and outside the room, but
9 I think you're asking about discomfort. So discomfort
10 would be reported either directly from the patient to
11 me, or the patient to the nurse.

12 DR. HAYES: And I understand there were
13 three stop sonication buttons.

14 DR. TEMPANY: There are, yes.

15 DR. HAYES: You, the patient, and the
16 nurse.

17 DR. TEMPANY: Yes.

18 DR. HAYES: And I wonder -- I didn't hear
19 too much discussion about indeed when they were used,
20 and if, in fact, how they correlated with any of these
21 adverse effects.

22 DR. TEMPANY: Right. Good question.

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1 They're used, and usually when it was used, it was
2 when the patient was experiencing severe sciatic nerve
3 pain, so she would stop it off. That's the most
4 common time it occurred.

5 DR. NOLLER: Thank you. Dr. Diamond and
6 Dr. Brill.

7 DR. DIAMOND: As far as potential other
8 mitigating factors that could be taken, beepers go
9 off, and phones ring, and I could see someone be
10 distracted and glance away when someone is moving or
11 when something else is happening. Maybe some of these
12 can be built as failsafes into the machine. The MRI
13 picks up motion, then it shuts off during the
14 sonication, or if picks up some of the cavitations, if
15 I understood that correctly, that it would
16 automatically shut off, rather than relying on an end
17 user who could be distracted momentarily.

18 DR. NOLLER: Dr. Brill.

19 DR. BRILL: Just another reflection now,
20 picking up what Dr. Wood said previously about the
21 neurolysis. It's my understanding in the FDA
22 presentation this morning, that at least with the

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1 thermal modeling, with a 90 second cool down that
2 there are two curves that are generated. The lower
3 curve, which is the best case scenario, there was a
4 variation of 39 to 42 degrees. And you just said that
5 for neurolysis you go to 42 degrees.

6 DR. WOOD: This potentially is a different
7 mechanism. That pulsed radio frequency, 500
8 kilohertz.

9 DR. BRILL: So if that's the case, she --

10 DR. WOOD: That may not be thermally
11 mediated. That could be mediated by impairment of the
12 electric neuro conduction potentially -- so that may
13 be a different mechanism.

14 DR. BRILL: So I'm bringing that up as a
15 point, as perhaps the 90 second interval may be
16 something that's worth looking at in the context of a
17 larger window of safety, if indeed the nerves are more
18 sensitive than realized to thermal effects.

19 DR. NOLLER: We have six minutes before
20 our break, but let's start on Number 6. Total
21 abdominal hysterectomy was selected as a control group
22 in this study in order to allow for comparison of

1 rates of recovery and serious adverse events between
2 ExAblate and what has been seen historically as the
3 standard of care for uterine fibroids. However, this
4 was not a randomized study, and ExAblate patients
5 differed significantly from TAH patients and BMI,
6 really prevalence, not incidence of diabetes mellitus,
7 hypertension, anemia, and other chronic conditions.
8 Are the results of this study sufficient to
9 demonstrate clinically meaningful comparisons
10 regarding the safety of the ExAblate procedure
11 compared to total abdominal hysterectomy?

12 I'd just like to mention there, it says
13 standard of care for uterine fibroids is hysterectomy.
14 That's certainly not true. The standard of care is
15 observation, but in patients with severe symptoms, TAH
16 has been a rather common procedure used. But the
17 question is, do we think that this is a meaningful
18 comparison.

19 Now again to -- we need to remember that
20 the study was designed in conjunction with the FDA, so
21 the sponsor did what was decided. But do we think
22 that what was done gives us a feeling that this is a

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1 procedure that gave meaningful clinical results? Yes,
2 Dr. Brown.

3 DR. BROWN: In my opinion it was -- short
4 answer, no. I don't -- to me in evaluating this,
5 comparing it to hysterectomy, that doesn't -- I don't
6 really quite get the clinical relevance of it. It's
7 like comparing -- you know, you're doing something
8 that you know is completely different and has a whole
9 different set of complications, that there's no way
10 you would see, but I don't know that that's really
11 germane to looking at the safety of this particular --

12 DR. NOLLER: Really efficacy we're on now.

13 DR. BROWN: Or the efficacy, but this is
14 clinically meaningful comparison regarding the safety
15 of ExAblate compared -- is that supposed to be
16 efficacy, that word? It says, "Are results of the
17 study sufficient to demonstrate clinically meaningful
18 comparison regarding the safety of ExAblate"?

19 DR. NOLLER: Yes, that does say safety,
20 doesn't it.

21 DR. BROWN: So to me, the answer to that
22 is no. I don't know why you would be shocked if --

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1 DR. NOLLER: The ExAblate, it had
2 certainly fewer complication than TAH, but you'd
3 expect that for anything, except maybe radical
4 hysterectomy.

5 DR. BROWN: No, but I mean it's a general
6 anesthetic. I mean, it's totally different.

7 DR. D'AGOSTINO: I mean, even the fact
8 that they had the patients at different locations as
9 opposed to the same location, I mean not only I think
10 was suggesting a randomized controlled trial against
11 a sham operation, but I mean, we do these things in
12 cancer. We do it in cardiovascular. We get
13 individuals who could have qualified for a particular
14 procedure, and we ask them if they'd be willing to try
15 some new procedure, and you possibly could have
16 randomized the two different procedures. But even in
17 that, if you didn't want to go through a randomization
18 same location, trying to do a propensity score
19 adjustment is just -- I mean, it's wishful thinking
20 when you only have something like 73 subjects.

21 DR. NOLLER: I guess the thing that
22 appealed to me about the different sites, even though

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1 normally I wouldn't think it's a good model, is that
2 if it weren't randomized, if it were at the same site,
3 I would think you'd have a terrible uncontrolled --

4 DR. D'AGOSTINO: Exactly, then you might.
5 But then you might be able to do some kind of a
6 propensity score adjustment because you have sort of
7 a similar group of subjects. You don't really know
8 what you have here.

9 The other thing that's bothering me is the
10 time on this here. Again, granted they're thinking of
11 six months, but the FDA is saying we want to follow
12 these individuals for three years, or we want you to
13 follow them for three years. By the end of the year,
14 the study has fallen apart. I mean, you have 23
15 people switching or taking an alternative treatment.
16 You have four who have taken a second focused
17 ultrasound, and you have 11 who had less than 10. So
18 if you forget the efficacy, if you wanted to talk
19 about safety, what is the safety, after six months or
20 after 12 months? You'd have different safety
21 comparison if you start saying what happens to these
22 individuals by the end of 12 months, because a number

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1 of them now are taking alternative procedures, and
2 unfortunately being blessed with all of the curses of
3 the more serious procedure. I really don't know what
4 we can make of this, personally.

5 DR. NOLLER: And it was pointed out before
6 the days of lost work and so forth for those that had
7 to have a hysterectomy, and were not added in. Mike.

8 DR. DIAMOND: Unfortunately, I think the
9 control group as it is is worthless in a word. But a
10 couple of people have made the comment that we should
11 not have considered the sham group here, and I think
12 that's a real viable option. I can envision a study
13 where patients would get on the machine, everything
14 would be going through. You either would or would not
15 turn the machine on to sonicate, and patients wouldn't
16 be told what was done or not. And obviously, this
17 would all be in the consent form. They know they'd
18 have a 50 percent chance or whatever it is of being
19 assigned to that arm, and they could be promised that
20 if they're in that arm, and then they decide they have
21 to go for further therapy, that at that point they
22 could be treated like that. There would be some

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1 patients that wouldn't participate, but I think there
2 would be many that would.

3 And with all due respect, the comment that
4 it's not ethical to randomize patients into it, now we
5 have a situation we're being forced to see whether
6 we're going to recommend or not this device. And we
7 may have end with patients going in in the future with
8 a device that's approved and being used, without truly
9 being demonstrated to be efficacious. And
10 unfortunately, it gets even worse because there are
11 other situations which have been looked at for pelvic
12 pain in women, both for uterine fibroids and adhesions
13 where placebo controlled studies have shown that at
14 three and six months follow-up, the placebo treated
15 group, again the patients weren't told whether they
16 were treated or not had benefits on severity of
17 symptoms scale. And so without a comparison arm to
18 assess the primary endpoint here, I don't know what
19 we're left with.

20 DR. NOLLER: Dr. Weeks.

21 DR. WEEKS: I would agree with Dr. Diamond
22 in terms of study design. And especially if it were

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1 a pre-hysterectomy type trial, where everyone
2 ultimately will get a hysterectomy say six months
3 later. As far as safety, comparing this to TAH, I
4 agree with Dr. Brown, I think is not really
5 appropriate and helpful. Given the constraints that
6 the sponsor had, my feeling is two key factors here.
7 First, some misunderstanding about the length of
8 follow-up, and I think we have to acknowledge that
9 that probably impacted their result. And the fact
10 that at the time, there weren't as many procedures for
11 uterine embolization, for example, et cetera. So my
12 feeling is I think safety has been diligently
13 monitored, and they put into place some mechanisms for
14 limiting the risk, so I almost see it as two separate
15 questions. Have they demonstrated an adequate or
16 reasonable degree of safety? Perhaps yes. It is
17 appropriate to compare TAH? I think the answer is no.

18 DR. NOLLER: Do you have a comment?

19 MS. MOONEY: I think I recall Dr. Stewart
20 saying that of the patients that were enrolled in the
21 trial, they all based upon their symptomatology would
22 have been candidates for hysterectomy procedure, so I

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1 think that from a clinical standpoint and from a
2 patient standpoint it is valid to say that a patient
3 was facing a choice clinically between hysterectomy
4 and something less invasive. And I think one of the
5 things we should not lose sight of is, I think we're
6 wrestling with the fact that it feels like apples and
7 oranges because we're comparing a surgical procedure
8 to something that's totally non-invasive.

9 I think we should be careful not to
10 penalize the device, so to speak, because it is non-
11 invasive versus surgery. I think the patient's actual
12 clinical choice here was between those two modalities,
13 again in the time frame when the study was set up, and
14 perhaps Dr. Stewart would like to comment on some of
15 the -- elaborate a little bit more on the discussion
16 that took place relative to sham versus separate --

17 DR. NOLLER: Give us just a second. I
18 think that's an important point, what Dr. Diamond
19 said. Certainly, there are multiple, multiple trials
20 that have shown long lasting good results in pelvic
21 pain, and this could be bleeding or pelvic pain as
22 symptoms, but from sham operations or placebo drugs,

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1 or whatever. It's tough to know what the real effect
2 of this is, particularly since 30, 33 percent of those
3 left in the study could have had something else done
4 by 12 months, so it's difficult. Yes.

5 DR. JANIK: I also agree. I think a sham
6 operation would clear a lot of these questions, both
7 on the validation study and statistically probably it
8 wouldn't take many patients to answer the question.
9 It could be a small number.

10 DR. D'AGOSTINO: What I was saying is I
11 don't even think you need to do a sham operation. You
12 could have done the idea that these are all going to
13 ultimately go to hysterectomy, and do randomization at
14 the beginning, hysterectomy or not, and then later on
15 go to hysterectomy. There are a number of designs
16 that could have been done. If you think the sham
17 procedure is ethically valid, then that's even better
18 procedure. I just don't buy at all the idea that you
19 can't do a randomized trial.

20 DR. JANIK: I think in this subset you
21 could find patients that are symptomatic, that they
22 often wait years before they get intervention. So if

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1 you get the right subgroup of people who are
2 symptomatic enough, but on the fence enough to do
3 something intermediate, I think it could be done.

4 DR. BRILL: I'd like to add that there
5 really is no correlate, because we have a procedure
6 which is this selective myomectomy, or selective
7 myolysis, or selected myoma destruction procedure, and
8 is this an abdominal myomectomy where you take one
9 myoma out and leave the rest behind or take the one
10 out that you prefer? Is this a myolysis where you
11 coagulate one and leave the others behind? I'm saying
12 to find a correlate with what's being done in the
13 study is impossible, because there is nothing that
14 we're doing on this level.

15 DR. NOLLER: Let's -- do you have one more
16 comment? Then we'll ask sponsor for a response and
17 then we'll break. Yes.

18 MS. MOONEY: Just one last comment. I
19 think that in terms of the patient satisfaction
20 scores, I believe they even had 12 months. Those were
21 somewhere upwards of three quarters of the patients
22 treated with the device still had some form of

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1 positive feedback or assessment.

2 DR. D'AGOSTINO: It was less than 50
3 percent. It was 44.

4 MS. MOONEY: On the patient satisfaction
5 scores?

6 DR. STEWART: Yes.

7 DR. NOLLER: Dr. Stewart.

8 DR. STEWART: Yes, Ebbie Stewart. We
9 concede that there is no perfect study design,
10 especially in this field, but we do feel we've
11 presented the optimal study that was feasible at the
12 time. And I think if we look at the history of
13 fibroid therapies and where we've gone in the past,
14 that this is a superior study design to that of many
15 of the procedures that have been introduced.

16 The Duke Evidence-Based Practice Report
17 talks about various surgical therapies, and really
18 comments that there is no evidence that there's
19 efficacy beyond 12 months for myomectomy or other
20 minimally invasive surgical procedures. Uterine
21 artery embolization is the clearest parallel
22 procedure. And to date, there are no published

1 studies of either randomized trials involving uterine
2 artery embolization and another technique, or even
3 significant parallel controls, that the studies that
4 led to FDA approval of embolic agents for uterine
5 artery embolization were based on generally six months
6 of data in a single study pair, so the fact that we
7 did do a contemporaneously assigned control group to
8 look for safety issues, we clearly didn't expect
9 hysterectomy to be the proper control for efficacy,
10 but to provide some mechanism of safety. And I think
11 the data that we've shown you today do show clearly
12 that women undergoing MR guided focused ultrasound
13 surgery have fewer safety complications than women
14 undergoing hysterectomy at the same time.

15 And regarding the possibility of
16 randomizing women pre-hysterectomy, that's in many
17 ways as close as we can get to our feasibility study.
18 In fact, we didn't want to allow anybody the option of
19 going on to focused ultrasound without being able to
20 confirm that they were going to hysterectomy. And
21 even that study design wasn't able to be carried out.
22 I think a sham study would also be facing the same

1 difficulties, and we realize that there are
2 limitations in the study design, but I think we did
3 learn very important things, and have proven the
4 safety of the procedure. And I think that we do have
5 significant efficacy, and like some newer therapies
6 that are being seen in medical treatments, there are
7 potentially groups of better responders and groups of
8 worst responders, but I think we've seen a subgroup of
9 patients who do get consistent long term results.

10 DR. NOLLER: We will now -- did you have
11 one comment?

12 MR. NEWMAN: I'd just like to say that
13 these issues of an appropriate control arm,
14 comparisons for safety, comparisons for efficacy,
15 randomization, sham treatments were all things that
16 were discussed a great deal with FDA during the design
17 of the study and things we wrestled with at great
18 length. And that's how we came to the negotiation of
19 the design of the study. And we believe within the
20 limitations that we were able to develop starting in
21 December of 2001, that we made the point that the
22 focused ultrasound as a treatment is safe. We

1 acknowledge the limitations when we're comparing it to
2 TAH, and we believe that the efficacy measurements
3 that are available to prove that it's an efficacious
4 treatment for uterine fibroid.

5 DR. NOLLER: Thank you. We will take a
6 break now until 5 minutes after 3, when we'll have an
7 open public hearing.

8 (Whereupon, the proceedings in the above-
9 entitled matter went off the record at 2:54:45 p.m.
10 and went back on the record at 3:06:30 p.m.)

11 DR. NOLLER: We'll now move on to the --
12 we'll interrupt our discussion of the nine questions
13 and have the open public hearing. I need to read a
14 statement to start the hearing.

15 Both the Food and Drug Administration and
16 the public believe in a transparent process for
17 information gathering and decision making. To ensure
18 such transparency at the open public hearing session
19 of the advisory committee meeting, FDA believes that
20 it's important to understand the context of an
21 individual's presentation. For this reason, FDA
22 encourages you, the open public hearing speaker, at

1 the beginning of your written or oral statement, to
2 advise the committee of any financial relationship
3 that you may have with the sponsor, its product, and
4 if known it's direct competitors. For example, this
5 financial information may include the sponsor's
6 payment of your travel, lodging or other expenses in
7 connection with your attendance at the meeting.

8 Likewise, FDA encourages you at the
9 beginning of your statement to advise the committee if
10 you do not have any such financial relationships. If
11 you choose not to address this issue of financial
12 relationships at the beginning of your statement, it
13 will not preclude you from speaking.

14 If there are people in attendance who
15 would like to speak, I would ask them to come forward,
16 state their name and any statement they wish to make
17 concerning these financial arrangements, and then
18 begin their presentation.

19 DR. SPIES: Thank you for allowing me to
20 speak. I'm Jim Spies and I'm from Georgetown. And
21 I'm here -- let me refer to my next slide.

22 DR. NOLLER: We can't hear you. I'm

1 sorry.

2 DR. SPIES: Oh, I'm sorry. I'm here
3 representing the Society of Interventional Radiology,
4 which has an interest in the subject of minimum
5 invasive treatments for fibroids, and specifically
6 uterine embolization. I have been a consultant in the
7 past and have spoken with this panel before in
8 evaluations of both Biosphere Medical Products and
9 Boston Scientific, and as many of you in the panel
10 might know, I have a significant interest in uterine
11 embolization which I think is probably a competing
12 technology. But certainly my primary goal here today,
13 I hope, is to discuss some of the issues related to
14 the questionnaire.

15 I was the principal author in developing
16 this questionnaire along with MEDTAP International.
17 Karin Coyne is here today, and we collaborated on
18 this, and did this based out of Georgetown and it was
19 developed here in Washington, D.C., so I think I may
20 be able to address some of the questions that the
21 panel has had regarding this.

22 There's no question that uterine sparing

1 therapies are a new paradigm for treatment of
2 fibroids, and I would actually agree that hysterectomy
3 is not a very good comparison because it's rapidly
4 going out of favor among many gynecologists as an
5 optimal treatment, although obviously still very
6 commonly done.

7 We've learned with embolization, one of
8 the reasons that we developed the questionnaire was
9 because there were no valid ways to measure outcome
10 from this. And really, it is symptom driven, and I
11 applaud the company, the sponsor for using this
12 questionnaire because they recognized early on that
13 what really matters are patients better. And, of
14 course, the Society does welcome new therapies for
15 fibroids and minimally invasive therapies, and we're
16 in clear support of comparative evaluation of this
17 therapy, for example, studies of embolization versus
18 this technology.

19 The change in uterine and fibroid volume
20 are key points in this, and we've alluded to this
21 before. The volume doesn't really matter. It does
22 not make very much difference. And we've done some

1 studies, and I'll show you some data regarding that.

2 Symptoms need measurement by a validated
3 question. That's why that was developed. The imaging
4 outcome really is a better predictor of recurrence.
5 You have to completely infarct the fibroids on
6 contrast enhanced MRI or they'll regrow.

7 So talking a little bit about the
8 questionnaire, this questionnaire was developed with
9 a grant from the research arm of the society of
10 interventional radiology with the specific intent of
11 assessing the effectiveness of embolization and other
12 therapies. And we had hoped that it would become sort
13 of lingua franca, something that everyone would use so
14 we'd be able to talk about scores and have some
15 meaningful comparison, because really there was no way
16 to do that previously. And I'm again pleased that the
17 sponsor has chosen to use this. There are some other
18 uses out there which I'll mention that are ongoing
19 which should help us to be able to put into context
20 the issue of what does a change of 10 points mean, or
21 20 points, or whatever.

22 There is no question that the symptom and

1 quality of life situation changes over time within a
2 women even without therapy, and so there's always
3 going to be some degree of fluctuation. This
4 particular instrument has a very high test/retest
5 reliability. You've already seen these so I'm just
6 going to skip through.

7 Basically, this can discriminate between
8 normal patients and abnormal patients or those with
9 fibroids, so you can see the bright green bars are the
10 normal patients, and the other green bars are the
11 abnormal patients. And this is from the original
12 validation.

13 Similarly, if you were to look at a
14 patient and say how severe are your symptoms - so if
15 you take a patient with fibroids and say are your
16 symptoms mild, moderate, severe, on a 10 point scale
17 and group them, this instrument can distinguish
18 between various levels of symptoms related to
19 fibroids. I should also mention that the original
20 validation of this include patients that have minimal
21 or no symptoms for fibroids. They just have confirmed
22 fibroids by a gynecologic examination, and they were

1 recruited in a gynecologist's office and in our own
2 practice with uterine embolization. So they had known
3 fibroids but not necessarily significant symptoms, so
4 that's why the scoring you see in the original
5 validation was in the range of about 44 because there
6 were some people that had relatively minor symptoms.

7 And I would agree with the sponsor when
8 they say that a score in the mid 60s is significant
9 symptoms. If you look at the scale and you go in the
10 mid point, which is the somewhat answer to eight
11 questions, you're going to get a score of 50. You go
12 up from there and you get a score of 75, so in the mid
13 60s is moderate to significant symptoms.

14 This is being currently used in a number
15 of longitudinal research programs. The largest is
16 sponsored by CIRREF, our organization, and it's done
17 in conjunction with DCRI which is the FIBROID
18 Registry, which has 3,000 women in it. We've just
19 completed a daily collection and one-year follow-up,
20 and that's going to be assessed fairly soon, probably
21 in the next few months. We're looking for short term
22 outcomes, as well.

1 Also, it's been used in a study of a
2 pharmaceutical company looking at the efficacy of
3 selective progesterone receptor modules in a life
4 study. And then my own use most recently, and I'm
5 just going to show a little bit of data to give you a
6 flavor of the changes you might see in a randomized
7 comparison of two different embolic materials for
8 uterine embolization. And that's the only data that
9 I have here today that I can actually show you that's
10 raw data, and part of it is going to be published.
11 It's been accepted for publication, will be published
12 in about two months.

13 The key questions for you, and you've been
14 asking them, is what is the normal score for the two
15 scales. And by the two scales I mean the symptom
16 scale, and then there is the total quality of life
17 scale. And the white represents a typical abnormal
18 squares for patients undergoing therapy, and we talked
19 a little bit about that. And one represents a
20 clinically meaningful change in scores. And I don't
21 have all the answers, but I'd just like to give you a
22 little bit of data.

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1 For those that are following this in the
2 handout that I passed out, I apologize the way this is
3 formatted, these numbers don't come out very well, but
4 if you look at this and you say well, if you took the
5 normals, and unfortunately the screen is off a little
6 bit, but if you take the normals which is the first
7 row - this is from the original validation, the
8 symptom score mean was 22.5. The quality of life
9 score was 86.

10 Now in a perfect world, in one we would
11 have zero score, no symptoms whatsoever, and they
12 would have a perfect quality of life. But most
13 quality of life studies have shown, particularly with
14 gynecologic symptoms, that most women do have some
15 gynecologic symptoms. They usually fluctuate with
16 their cycle, bloating, pressure, discomfort, a variety
17 of different things that are normal physiologic
18 events.

19 If you took the fibroid patients from that
20 original scoring, you got a score of 44. The quality
21 of life score was 62, so they had a diminished quality
22 of life based on the increased amount of symptoms

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1 they're having associated with their scores.

2 Then in this most recent study that I've
3 done in which we're taking patients that have
4 significant fibroids that are going to undergo uterine
5 embolization, our mean score for that group of 100
6 patients was 53.7 with a total quality of life score
7 of 52. So again, they are somewhat more symptomatic.
8 Now that's to compare to the sponsor study where
9 they're in the mid 60s at baseline, so their patients,
10 if anything, were slightly more symptomatic than this.

11 This again is that study that I've just
12 alluded to that we completed at Georgetown, and we
13 looked at 100 patients and randomized 50 to two
14 different embolic materials, three months and 12
15 months. We have not completed the 12 month grid,
16 although it is already is statistically significant.
17 But I'm not presenting that because I don't have all
18 the numbers.

19 For the three numbers, and again I think
20 this is a misprint. It should be 53.7, but the
21 symptom score, I just alluded to this, was in the 50s,
22 standard deviation of 22. Three months later after

1 uterine embolization the score was 21. Now with the
2 sponsor study it was in the mid 30s. They started
3 higher, they ended higher, and that's one of the
4 questions, is a score that's 35 or 37 adequate
5 improvement? And I don't have the answer. It
6 certainly is moderate improvement, but this symptom
7 score is normal. If you go back to the original
8 validation, 22 is a symptom score the patients had.
9 This is normalized.

10 The quality of life score was a day long
11 which is more or less in the same range as the normal
12 score, so just to give you some feeling of what
13 another therapy can actually do. Unfortunately, this
14 doesn't project on this particular computer.

15 What I would say about this is that on all
16 the scales, there are six step scales, and the total
17 quality of life scale, and all the symptoms score, all
18 of them were statistically significantly improved with
19 this comparative study that we did.

20 Now the other thing I'd just like to
21 concentrate on is to talk a little bit about -- this
22 is using the criteria of the sponsor. I took that

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1 same set of 100 patients, and I said how many of those
2 patients meet the criteria that leads to 10 point
3 improved symptoms score, and you can see that the
4 proportion improved just in pure portion, the 78 out
5 of 94 that we had the complete questionnaire on, 83
6 percent. There's was about 70 percent, so again we're
7 seeing similar kinds of results.

8 If we go from an intent-to-treat basis,
9 look at the entire sample, it's 84 percent without
10 complete data. HRQOL scores again are similar.
11 They're about 83 percent or so. It's a similar
12 number, although we don't again have complete data, so
13 I can't give the intention-to-treat that one year.
14 So in general, embolization works. This is a way that
15 you can measure. Now this obviously would have been
16 different if we put 15 or 20, and really what has to
17 happen with a large data set is you have to do some
18 modeling, and sort of look appropriate cutoffs.

19 The other thing I'd just like to take a
20 couple of minutes to talk about is the imaging outcome
21 because it's very germane to this. Focused ultrasound
22 at this time is not actively trying to infarct the

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1 entire fibroid, and it's reasonable for safety
2 considerations, et cetera. And I recognize that they
3 were very limited in what they're allowed to do under
4 this protocol. And in fact, it's entirely possible
5 that the symptom score would have improved
6 significantly more had they been allowed to do more
7 complete therapy, so I don't think you can look
8 exactly at the results with their hands tied behind
9 their back and make a complete judgment.

10 What we've learned though from
11 embolization sort of by a hard lesson is that you have
12 to completely infarct the fibroids to have good long-
13 term outcome. Short-term outcome, you can injure
14 them, infarct half of them or a third of them, you'd
15 probably do pretty well. But long-term, you've got
16 more of a problem. Failures and early recurrences
17 relate to the regrowth of uninfarcted large or key
18 fibroids. Late recurrence is generally due to the
19 growth of small incompletely infarcted fibroids at the
20 original treatment or new fibroids, and that's with
21 embolization. But it probably applies to this
22 therapy, radio frequency ablation or any others.

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1 So the key things to long-term outcome is
2 not the volume reduction. And there's a reference
3 there - we showed in a group of 200 patients that it
4 doesn't matter how much it shrinks. You're likely to
5 have pressure or other symptoms go away, it is the
6 same. What matters is you have to completely infarct
7 the fibroids, and particularly long-term. And we just
8 published this paper about two months ago by Dr.
9 Pelage, myself, and a group at Georgetown looking at
10 that particular issue.

11 I just want to give you two examples. I
12 don't have a pointer, I apologize. If you look at a
13 series of sagittal images here, the first one is a
14 non-contrast image. If it were contrast, most of the
15 uterus would be white. All the fibroids subsequently
16 are all black. They're rounded. They're getting
17 progressively smaller, and you can see that three
18 years out they're all completely infarcted and they
19 continue to shrink. There was no symptom recurrence
20 in this patient. This is one of the patients from the
21 study I just showed you. We had 20 patients with
22 three-year imaging follow-up, 17 of them look more or

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1 less like this. Three of them look more like this.

2 This is a patient, you can see in the pre-
3 image, the first at the top left, large fibroid that
4 is completely vascularized. At three months, you can
5 see that almost all of this fibroid is completely
6 infarcted, but there are little ridges there that are
7 perfused. And if you then go to a year and two years,
8 which is the first at the left on the bottom, three
9 years and four years, you can see that that fibroid is
10 progressively regrowing. That's despite the fact that
11 this fibroid is smaller at the end than it was at the
12 beginning. The uterus is much smaller than it was at
13 the beginning, so size doesn't matter. What matters
14 is this is vascularized. This patient's symptoms came
15 back between two and two and a half years. She's now
16 been retreated actually a little over four years after
17 her procedure. And if I had a pointer I would show
18 you just in the last image there is -- that is a new
19 fibroid. We've now shown with this and other studies
20 that you can develop new fibroids after uterine
21 embolization, which is not very surprising. Of
22 course, that would be with ultrasound ablation, as

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1 well.

2 So I would bring to the table some
3 moderate concerns regarding labeling in this
4 particular device or others which you're looking at a
5 uterine sparing therapy. The FDA by nature, and these
6 studies have been mostly focused on short-term
7 efficacy and safety. I have participated in studies
8 for embolization which are the same way looking at
9 three month, six month, one-year data, but the early
10 recurrence is going to be high if you don't completely
11 infarct the fibroid.

12 Now that brings up the question what
13 really is efficacy. Is efficacy six months, is it a
14 year, is it two years. Many treatments have good
15 short-term benefit, and clearly uterine embolization
16 is among them. It is important, I think, to consider
17 the two to five year effect.

18 We generally now are moving in the
19 direction of uterine embolization because if you're
20 not better for a year, it's a failed procedure. If
21 you're going to have something -- we're looking at the
22 reaction of at least a year of benefit, and frankly,

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1 it would be much better to have it go much longer.

2 I would just conclude by saying that
3 first, I think that the evaluation of high frequency
4 ultrasound does benefit from the use of this
5 questionnaire. I applaud the company because they
6 took on that questionnaire at a time when we didn't
7 have a lot of data, and they are correct, there is not
8 a lot of data out there yet. It's in the pipeline.
9 It's going to be published in terms of the treatment
10 effect that you can detect with the instrument.

11 The results need to be considered in the
12 context of the therapies that we're using some
13 measure. So in other words, you're going to say
14 what's better, embolization or whatever. You can't
15 take the numbers and directly compare them, but
16 certainly it does provide you the basis of doing
17 comparative studies. And then I would again emphasize
18 the issues related to contrast enhanced MRI. And
19 thank you for your attention. I appreciate it.

20 DR. NOLLER: Thank you. We have another
21 presentation that will be read by Ms. Luckner, our
22 consumer representative.

1 MS. LUCKNER: "To the members of the FDA
2 Acceptance of Gynecological Devices Panel Committee,
3 my name is Carla Dionne, and I am the Executive
4 Director of the National Uterine Fibroid Foundation.
5 We are located in Colorado Springs, Colorado, and
6 represent the only national non-profit patient
7 education and advocacy group specifically representing
8 women with fibroids in the United States. Thank you
9 for the opportunity to submit my testimony today on a
10 subject of a tremendous importance to the health and
11 welfare of women with uterine fibroids.

12 Although I cannot attend today's meeting,
13 would like to present a few issues for the panel to
14 consider when making recommendations for potential
15 approval of the InSightec ExAblate 2000 for the
16 treatment of uterine fibroids.

17 Based on the limited information made
18 publicly available June 2nd, 2004 regarding this
19 study, the following areas are of great concern.
20 Safety and efficacy.

21 Typically, the clinical trial recruitment
22 of a motivated patient population can minimize loss to

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1 follow-up, and provide more extensive information.
2 This particular group of women who underwent focused
3 ultrasound treatment for symptomatic fibroids should
4 have been an incredibly low risk group for loss to
5 follow-up. It is, therefore, quite surprising to see
6 a nearly 30 percent loss rate within six months, a
7 loss rate of 60 percent at 12 months, and an
8 additional 20 percent of the final group not lost to
9 follow-up who went on to a secondary alternative
10 procedure.

11 The FDA has previously indicated that loss
12 to follow-up of 15 percent or more make the
13 determination of safety and efficacy difficult to
14 assess. And as such, the maximum calculated as
15 acceptable is generally 15 percent. It would seem
16 loss to follow-up rates of 30 percent at six months,
17 and 60 percent at 12 months would completely negate
18 the results of this study in terms of truly
19 determining safety and effectiveness.

20 Under the circumstances, and in
21 consideration of the desperate attempts women make to
22 avoid surgical intervention, it is extremely

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1 questionable as to why so many women would be lost to
2 follow-up so soon after treatment. It is critical for
3 the clinical investigators involved in this study to
4 provide more information about follow-up for these
5 women."

6 There are pages more, Mr. Chairman. Do
7 you want --

8 DR. NOLLER: Are there any other points
9 that are --

10 MS. LUCKNER: Let me just pull one point
11 out, and then I will suggest the several other points
12 go on to labeling and training, and I can read them at
13 that time. And then go on for post-market study.

14 DR. NOLLER: Thank you.

15 MS. LUCKNER: But let me just read one
16 other piece. "In terms of efficacy, the 14 percent
17 volume reduction at six months is disappointing, at
18 best. Further, the decline in average percentage of
19 fibroid shrinkage at 12 months as 9.4 is abysmal.
20 Based on the data submitted regarding loss to follow-
21 up, subsequent alternative procedures, potential for
22 increased risk and subsequent procedures, and the

1 overall decline in the average volume reduction, the
2 cost benefit analysis must truly be questionable here.

3 Is this an appropriate treatment for women
4 with systematic uterine fibroids? Will women
5 desperate to avoid surgical intervention by any means
6 possible truly understand the potential risks involved
7 with undergoing this procedure"?

8 DR. NOLLER: Thank you.

9 MS. LUCKNER: Thank you.

10 DR. NOLLER: I'm sorry. We can't read it
11 later. Are there any other points that are important
12 or pertinent?

13 MS. LUCKNER: I'm trying to be objective.

14 DR. NOLLER: Yes.

15 MS. LUCKNER: I think the labeling and
16 training. There's a discussion of the exclusionary
17 consideration, and I think that that will be picked up
18 by the panel as I -- I just received this now, so I
19 think that will be picked up by the panel. There are
20 two different lists of what should be excluded.
21 There's discussion about what training requirements
22 are.

1 DR. NOLLER: Well, I have been instructed
2 to ask you to read the whole thing.

3 MS. LUCKNER: I'd be delighted to. Let me
4 go back and figure out where I left off.

5 "In addition, in an additional review of
6 the initial phases of the study where women underwent
7 hysterectomy after HIFUS, there were seemingly
8 inordinate number of patients who developed post
9 operative hematomas requiring surgical drainage.

10 IN addition, due to incisional bleeding,
11 one patient required ligation of a single uterine
12 artery. During the current study under review, if
13 HIFUS is non-durable for a great many women, what are
14 the subsequent surgical risks? Has surgical or
15 embolization risks increase due to the treatment with
16 HIFUS? If so, at what ratio, and what would the
17 severity of that potential risk truly be? Would
18 undergoing HIFUS become a contraindication to
19 myomectomy or embolization?

20 From the Agency of Healthcare Research and
21 Quality, AHRQ, based on the 1997 healthcare cost
22 utilization project, state in-patient database for 19

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1 states and post operative hemorrhages or hematoma rate
2 was 1.61 per thousand population at risk. There are
3 other references on the same topic.

4 DR. NOLLER: Thank you.

5 MS. LUCKNER: It would seem that
6 hysterectomy after the HIFUS group had an incident
7 ratio significantly higher than the norm per the
8 average. However, given the small number of women
9 studied who subsequently underwent hysterectomy, only
10 a larger study of women undergoing subsequent surgical
11 treatment would potentially offer more conclusive
12 information on this issue.

13 Given this, an incredibly critical
14 question remains unanswered. If HIFUS does not prove
15 to be durable long-term, greater than one year for
16 women, has undergoing the treatment compromised the
17 potential for subsequently undergoing a more durable
18 treatment safely, such as hysterectomy or myomectomy,
19 or even embolization?"

20 I'm reading about labeling now?

21 DR. NOLLER: Please.

22 MS. LUCKNER: Okay. Labeling and

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1 training. "One, exclusionary considerations. Patient
2 exclusionary criteria appears to be absent from public
3 review, but it is absolutely essential to the very
4 offering of this to women with fibroids. The
5 following exclusionary items should be reviewed for
6 potential dissemination to the medical community
7 treating women with fibroids, and to the general
8 public of women with uterine fibroids who may be
9 considering this treatment option for symptomatic
10 fibroids.

11 One, pediculated submucosa or subserosa
12 fibroids. Fibroids smaller than 4 cms or larger than
13 10 cms, presence of more than three to four fibroids,
14 presence of abdominal pelvic scars of keloids from
15 prior treatment, fibroids located too close to the
16 bladder, bowel or bone within 4 centimeters,
17 Hematocrit level less than 25 percent, excessive fat
18 and/or muscle in the abdomen, presence of adenomyosis,
19 desired fertility positive pregnancy test.

20 In addition, the following exclusionary
21 items related to ultrasound contrast and MRI should be
22 reviewed for dissemination; contrast allergies,

1 impaired renal function, claustrophobia, minus 15
2 percent of the population has -- give or take 15
3 percent of the population has claustrophobia severe
4 enough not to tolerate the enclosure of an MRI,
5 presence of any metallic substance or implanted
6 material such as heart pacemaker, surgical clips from
7 prior surgery sometimes applied during C-section or
8 myomectomy to the uterine artery or by a tubal
9 ligation, insulin pumps, cochlear implants, jewelry.

10 Presence of abdominal pelvic tattoos.
11 Depending on the location, they may contain enough
12 trace elements of metal so as to interfere with the
13 clarity of the MRI. Weight girth of no greater than
14 350 pounds table limit, but abdominal girth limit
15 might place this at no greater than 250 to 300 pounds
16 depending on the individual."

17 The next category is called training.
18 What are the potential plans for radiology and
19 gynecological training and certification for the
20 InSightec Albate 2000? Given exclusionary factors and
21 what appears to be a learning curve based on the
22 trials to date on selecting appropriate patients and

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1 using this equipment in the treatment of symptomatic
2 uterine fibroids. It is of tremendous concern that an
3 appropriate training and certification plan be firmly
4 in place prior to additional installation and use of
5 this equipment."

6 Post market study, and it's only another
7 page. "Given the poor showing of data presented for
8 this clinical trial, in consideration of FDA approval
9 of the InSightec Ablate 2000, this device has simply
10 failed to provide enough post treatment patient
11 information on its safety and efficacy in the
12 treatment of women with symptomatic uterine fibroids.
13 In short, the InSightec ExAblate 2000 should not
14 receive FDA approval at this time based on the data
15 presented, and with the continued outstanding concerns
16 over patient safety and efficacy.

17 It would be the recommendation of the
18 National Uterine Fibroid Foundation that this device
19 continue to be followed pre-market for an additional
20 year prior to subsequent review by the FDA. However,
21 given the loss to follow-up rate currently identified,
22 will there be any patients remaining from the pivotal

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1 study one year from now who are not also lost to
2 follow-up? Will there be any additional effort to
3 report on what exactly occurred to those patients lost
4 to follow-up? Did they ultimately undergo an
5 alternative procedure?

6 Furthermore, if the average percent of
7 fibroid shrinkage declines any further, will there be
8 a single patient left who is clinically versus
9 technically successively treated with HIFUS?

10 It would be our further recommendation
11 that the members of this panel consider the absolute
12 need for the design of a new study protocol with an
13 increased awareness of the potential for loss to
14 follow-up, exclusionary factors, and the risk to
15 subsequent procedures required for the potential
16 clinical treatment failure of HIFUS. Preferably this
17 study would not be a comparative study to a
18 hysterectomy, but rather comparative to other uterine
19 sparing treatments, and matching for appropriate
20 patient controls.

21 The Cardiovascular and Interventional
22 Radiology Research and Educational Foundation and the

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1 Society of Interventional Radiology, in cooperation
2 with Duke Clinical Research Institute have established
3 the uterine artery embolization fibroid registry for
4 outcome data. The purpose of the fibroid registry is
5 to specifically assess the durability, impact on
6 fertility, and the quality of life, and to obtain data
7 which would allow researchers to compare UAE to other
8 fibroid therapies.

9 Due to the number of patients undergoing
10 the non-surgical uterine sparing treatment of uterine
11 fibroid embolization, there is an abundance of
12 collected data for this treatment modality. This
13 would distinctly set UFE apart from hysterectomy as a
14 much more appropriate study group for comparison to
15 HIFUS than hysterectomy, and it would be our
16 recommendation that this be reviewed for
17 consideration. Respectfully submitted, Carla Dionne,
18 Executive Director, National Uterine Fibroid
19 Foundation, Colorado Springs, Colorado."

20 DR. NOLLER: Thank you for reading that.
21 We've now used all of the time for the open public
22 hearing. For panel members, what we will do is to go

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1 through the last three questions. At the end of that
2 time, I'm going to ask the panel if there are other
3 questions that you'd like to pose to the sponsor that
4 you did not get a chance to ask previously.

5 Then we will allow the sponsor to sort of
6 sum up and present answers to questions that haven't
7 been asked before or address points that haven't been
8 made. And then we will go into the recommendation
9 phase, the voting phase. So let's go to Question 7,
10 labeling and training.

11 Does the panel have any comments on the
12 labeling provided by the sponsor? Does the panel have
13 specific recommendations related to the proposed
14 indications, contraindications, warnings, precautions,
15 adverse events, clinical study?

16 I'm going to instruct the panel that we
17 aren't looking for wordsmithing things here, we're
18 looking for major concerns, things that were omitted
19 or introduced that are clearly incorrect. I would
20 also like to ask the sponsor to specifically address
21 the question that's asked, not to do a summing up or
22 get off on other related issues. So number 7,

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1 indications, contraindications, warnings, precautions,
2 adverse events, and clinical study. Any comment?
3 Yes, sir.

4 DR. SOLOMON: I think the prescribing
5 information should include more detail as far as who
6 you are excluding, meaning patients that have dense
7 calcifications or patients who have intestines in th
8 way, or there should be more warnings here as to
9 clarifying who you need to screen for. It may be more
10 difficult to get patients who have fibroids that are
11 lower than those that are more at the fundus, so I
12 think more detail as to who they should include should
13 be included.

14 DR. NOLLER: I'd like to make one comment
15 there. I had sort of mentioned this before, but in
16 the patient brochure and some other parts of the
17 labeling, there are several times that the standard of
18 care is mentioned. It's hysterectomy. As I said
19 before, that absolutely is not. The standard of care
20 is observation. For patients with serious
21 complications of fibroids, then you might consider
22 doing more. And I would probably avoid using the term

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1 "standard of care", since it really doesn't mean much
2 except in a courtroom, but be more specific about the
3 labeling.

4 DR. JANIK: I agree that we need to have
5 more clarification on indications, and indications
6 would be number of fibroids, optimal location of the
7 fibroids, in addition to exclusions that were
8 mentioned, so it's not real clear who would be best
9 qualified for this.

10 DR. NOLLER: Dr. Brown.

11 DR. BROWN: Two comments. I would think
12 that given the data we heard today that the issue of
13 nerve injury should be included and labeling under
14 potential adverse events that says back or leg pain.
15 I think that's a very different thing than saying
16 nerve injury.

17 And I also, relevant to my other question
18 that did not get addressed about the diversity, lack
19 of diversity in the study population, there's specific
20 mention in the labeling that the device -- the study
21 results did not show any decreased effectiveness in
22 patients based on race, age, menstrual status, BMI, or

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1 fibroid type. And I just really question whether
2 there was really enough power in the study to talk
3 about differences in any of those factors. I don't
4 think that's really a valid statement, so I would
5 suggest that that -- I don't know if that -- because
6 it didn't seem to me this study had the power to say
7 that those things were not factors.

8 DR. NOLLER: Dr. Roberts.

9 DR. ROBERTS: Well, when I read over these
10 instructions for use, quite frankly I think it needs
11 a lot of work by the agency and the sponsor. I mean,
12 I think that somewhere in here it's going to have to
13 be clear what this study looked at, and what it didn't
14 look at. And I think there's a lot of things, one of
15 the things is I think it's going to be important to
16 put in here what at least the pivotal study was or, in
17 fact, what the expanded study was, so that even if you
18 go to the expanded study, that the limitation of
19 sonication was 180 minutes, that there was a 15
20 millimeter margin to the serosal surface, that the
21 treatment volume was up to 50 percent if that's what
22 you're going to go for, that maybe you could do more

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1 than one treatment, but it wasn't done any more than
2 one treatment, if there was total treatment to a
3 volume maximum of 150 Ccs. I mean, I think somewhere
4 in here that's going to have to be spelled out because
5 presumably that's going to be the only place that at
6 least it's written down some place.

7 And I think the other thing that really is
8 important sort of goes to what was said before, which
9 is it's kind of lost in here that it really needs to
10 be 4 centimeters away from the sacrum and the
11 importance of making sure that it's away from the
12 sacral nerve plexus. It really needs to be standing
13 out in here.

14 And I think the other thing that somebody
15 is going to have to kind of look at and try and figure
16 it out is that given the numbers that we saw that the
17 non-perfused volume was more than - essentially at
18 least in the study - was more than twice the region of
19 treatment, and that the question is going to be how do
20 you counsel physicians about what they're going to do?
21 So if they go more than that, what does that mean? We
22 don't know, but somehow that's going to have to get in

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1 there.

2 DR. NOLLER: Dr. Wood.

3 DR. WOOD: It would be nice to see a
4 section on the importance of the light sedation or
5 something besides just the words "conscious sedation",
6 the importance of constant feedback from the patients,
7 that it hasn't been used with general anesthesia or
8 deep sedation, and that could pose increased risk.

9 DR. NOLLER: Dr. Diamond.

10 DR. DIAMOND: A couple of things, in the
11 essential prescribing information under training, it
12 states that "Training in ExAblate is provided by
13 InSightec." I think that probably ought to be
14 stronger, really along the lines of what Mr. Newman
15 presented to us during his presentation of what would
16 be required as part of the training process, and who
17 would be involved in it, as a prerequisite for
18 utilizing it.

19 In the brochure for the patient, it
20 currently states that this process will be repeated to
21 treat your entire fibroid, and that's not what is
22 intended at least at this point, so that needs to be

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1 modified. And then at the end of that, I think it
2 needs to be provided -- it needs to be real clear that
3 this may not provide patient benefit in selected
4 patients, so they may not see a benefit. And if they
5 are going to see an improvement, what kind of
6 improvement should they expect and over what time is
7 it likely to be present for.

8 DR. NOLLER: Others? Yes.

9 MS. LUCKNER: There's no mention of the
10 scar issue or the size of the patients that may not be
11 eligible for this. And that big issue has been
12 discussed several times by the panel.

13 DR. NOLLER: Others?

14 DR. WOOD: There's one line about scaring
15 or surgical clips in the individualization of
16 treatment section. But it raises a question that we
17 didn't address. Were patients with previous C-
18 sections stratified in any way according to
19 complications?

20 DR. NOLLER: Dr. Roberts.

21 DR. ROBERTS: The only thing I was going
22 to say is in terms of the patient manual. In the

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1 long-term effects or risks it says "back or leg pain
2 or weakness." I think it probably ought to be a
3 little stronger than that, and basically say it's
4 nerve damage, because that's what we're really talking
5 about. I mean, if they just think well, their leg is
6 going to hurt, that doesn't really -- I don't think it
7 really answers what might be potentially anyway, a
8 serious problem.

9 DR. NOLLER: And if you read the labeling
10 on aspirin or anything it's your head may fall off,
11 your arms may fall off. It goes on, and on, and on.
12 Yes, Dr. Brown.

13 DR. BROWN: Just one other comment about
14 the patient manual. I think (a) it's way too
15 detailed. It's at extremely high reading level, and
16 I also would take exception to the table where you're
17 comparing alternatives, because for example, it says
18 that hormone therapy is only effective for six to
19 twelve months. Well, we've just heard that this is
20 only effective for six to twelve months, so that just
21 needs to be completely reworked, and looking at what
22 are the important messages you're trying to get to the

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1 patient, try to make them understand what the
2 procedure is, what the risks are, and what the
3 potential benefits are. I'm not sure how important it
4 is in your document to compare other treatments.
5 That's really the job of their physician who's
6 counseling them about what choice to make.

7 DR. NOLLER: Others? If not, we'll move
8 on to Question 8. For that point, is there any
9 sponsor -- we didn't really ask any specific question.
10 Number 8, FDA and the sponsor agreed upon procedural
11 requirements during the pivotal trial, and in the
12 continued access study to mitigate safety-related
13 concerns that are shown in the attached table. Is the
14 ExAblate training system sufficient to ensure that the
15 proposed mitigations are followed? Discussion?

16 DR. ASCHER: I have a comment.

17 DR. NOLLER: Yes.

18 DR. ASCHER: Given mitigation and all the
19 stuff we've learned today, I wonder how the sponsor
20 came up with the training recommendations. At least
21 my reading of it, it's one session. Potentially you
22 phantom and then potentially you might see a patient

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