

1 able to accrue since you've been doing this study for
2 some time on those two parameters?

3 DR. diZEREGA: That's absolutely correct,
4 Dr. Roy. A number of people have published or
5 validated the clinical utility of the AFS scoring
6 system, and it certainly occurred to us to try to
7 collect particularly fertility data in this
8 population, and especially when the study was
9 finalized, the last patient had her second look
10 laparoscopy.

11 However, we unfortunately did not organize
12 the protocol in a way that allowed for meaningful
13 analysis of that type of data. There is no evaluation
14 of any male factor. There's no evaluation of a coital
15 frequency or timing of intercourse. There's no
16 evaluation of ovulation, ovulatory rates or ovulatory
17 stimulation by exogenous medication.

18 There are patients who quite clearly said
19 that they were infertile. They would like to be
20 fertile, but not now, at some time, a date certain.

21 And since this multi-factorial disease,
22 infertility, was simply not part of the intent of the

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1 study and because there are so many variables that we
2 did not control for, we did not go back and try to
3 evaluate that.

4 DR. ROY: What about pain?

5 DR. diZEREGA: Pain is actually even more
6 of a pain.

7 (Laughter.)

8 DR. diZEREGA: At least with pregnancy
9 there is an HCG level or a baby that you can talk
10 about as an endpoint. In terms of pain, we have been
11 very unsuccessful in thinking about ways to measure
12 that from a clinical perspective.

13 We thought perhaps doing conscious
14 sedation mini-laparoscopy might be helpful. That
15 didn't work out. We looked at different analogue
16 scores and that didn't work out.

17 And so I think as difficult as it is to
18 assess fertility in these types of situations, pain is
19 even more difficult.

20 CHAIRMAN WHALEN: Dr. McCauley.

21 DR. McCAULEY: Just a quick follow-up
22 question. After correction of your allergic reactions

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1 to lactated Ringer's, did you reanalyze the data to
2 see whether there was a difference between INTERGEL
3 and your control?

4 DR. diZEREGA: No, sir, we did not
5 reanalyze the data after correction of the allergic
6 reactions.

7 CHAIRMAN WHALEN: Are there any other
8 questions from the panel?

9 DR. diZEREGA: Did you want to comment,
10 Doug?

11 DR. JOHNS: Well, on the allergic reaction
12 question, I think there was only one, possibly two
13 that would have been considered allergic reactions to
14 something other than seasonal allergies. One I recall
15 was a control patient who had an allergy to Tums, and
16 there was another patient that had itching in the
17 postoperative period. So it would have been like one
18 or two patients at most.

19 To answer Dr. DeMets' question, I can
20 display for you another graph the patients who were
21 not treated or they are in the clinical summary that
22 was sent to you from I'm not sure which book it would

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1 be in what was sent to you, but in our clinical
2 summary it's on page 23.

3 The most common reason for patients
4 entering the OR and then not being included in the
5 study was for more than 12 of the sites having
6 adhesions or a site being removed.

7 MR. DeMETS: I wasn't clear. Actually I
8 didn't mean -- I said "site." I meant -- I was
9 thinking site in terms of center.

10 DR. JOHNS: Center?

11 DR. DeMETS: In other words, did all of
12 this happen in one or two centers is my question or
13 was it one center?

14 DR. JOHNS: No, it was pretty well
15 scattered.

16 CHAIRMAN WHALEN: Thank you then.

17 Dr. Krause has an announcement.

18 DR. KRAUSE: I was informed that since the
19 FDA section, which is against the wall opposite the
20 door, is not completely full in the afternoon, because
21 of the overflow of attendees, any seats not used in
22 the FDA section will be available for the public.

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1 Thank you.

2 CHAIRMAN WHALEN: Thank you, Dr. Krause.

3 We're about 20 minutes ahead of schedule.

4 So we will at this time adjourn for lunch. Following

5 the lunch break, we will have the FDA's presentation,

6 and I would ask that everyone please reconvene at a

7 time sufficient to begin that presentation promptly at

8 1:15 p.m.

9 Thank you.

10 (Whereupon, at 12:11 p.m., the meeting was

11 recessed for lunch, to reconvene at 1:15 p.m., the

12 same day.)

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1 I'd like to start out by just briefly
2 reading the company's indications for use. "The
3 INTERGEL adhesion prevention solution is indicated for
4 use as an intraperitoneal instillate" --

5 I tried that. It didn't work. Oh, there
6 it goes. Now it will move.

7 -- "following peritoneal cavity surgery.
8 It has been shown to reduce the incidence, extent, and
9 severity of adhesions throughout the abdominal cavity
10 when used as an adjunct to good surgical technique."

11 There'll be a question on that later, and
12 I don't mean that as a joke.

13 The device description, the company has
14 already basically described the product. However, I
15 will just briefly go over it again.

16 INTERGEL is a sterile, amber colored
17 viscous, nonpyrogenic, aqueous solution composed of
18 hyaluronic acid that is ionically cross-linked with
19 ferric ions. The solution also includes a number of
20 other materials as you can see up there simply for pH
21 balance, and it's supplied in a 300 milliliter bellows
22 bottle.

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1 This slide kind of got reversed in its
2 polarity. So I can't see it. However, it basically
3 just says that all of the biocompatibility and
4 toxicity studies were performed in accordance with
5 good laboratory procedures as specified in the Federal
6 Register by the FDA.

7 The biocompatibility studies that were
8 performed and passed by the product are in vitro acute
9 toxicity, in vivo acute toxicity, multiple dose
10 subchronic toxicity, dermal sensitization,
11 pyrogenicity, menolysis, and reproductive toxicity.

12 I thought I would also mention that the
13 company did extensive testing on formulations and
14 preclinical efficacy. I didn't think it would be --
15 would take a long time to go through all of that.
16 Suffice it to say that the product was effective in
17 animal studies, and the formulation studies were
18 extensive to find the best formula that worked.

19 There were a few interesting things that
20 we saw when we looked through the preclinical data
21 that I thought I should appraise or bring up before
22 the panel. One of these was some of the further

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1 studies done in the in vivo acute toxicity vein, and
2 the studies that were performed, and there were many,
3 basically were acute toxicity in mice, acute toxicity
4 in rats, acute toxicity in rabbits, and acute toxicity
5 in dogs.

6 I thought I would just summarize the
7 results. As long as the installation amounts of
8 INTERGEL were in the range of what patients saw during
9 the clinical trial, which was five milliliters per
10 kilogram, or approximately 300 milliliters per 130
11 pound patient, there were no observable deleterious
12 effects.

13 However, for smaller animals, which were
14 sexually immature, installation of volumes
15 approximately tenfold greater and higher than the
16 equivalent dose that was used in the trial resulted in
17 some fatalities, and also at these higher doses, there
18 were effects on body weight, transient clinical signs
19 of toxicity, and some systemic toxicity.

20 Another study or group of studies that FDA
21 found interesting were the reproductive studies where
22 higher doses, again, were employed, and in some of

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1 these you could induce reductions in the mean number
2 of implantation sites, viable fetuses, and live litter
3 size when applied at doses of five, 15, and 25.
4 However, only the 25 milliliters per kilogram dose was
5 statistically relevant, and those were -- 25
6 milliliters per kilogram is five times above the
7 clinical dose.

8 The difference in live litter size and
9 viable fetuses was not accounted for by the death of
10 any fetuses.

11 The effect could essentially be eliminated
12 by allowing seven days of nontreatment between the
13 last application of INTERGEL, and what's important to
14 realize here is that the product was applied at 25
15 milliliters per kilogram multiple times. It wasn't
16 just one application. It was done four to five times
17 and two to three days apart.

18 Then if you allowed seven days between the
19 final application and cohabitation of the rats,
20 although viable fetuses and implantation sites were
21 still slightly less than control, the differences were
22 not statistically significant. No statistically

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1 significant treatment related changes were observed in
2 animals treated with clinically equivalent dose of
3 five milliliters per kilogram.

4 The last aspect of the preclinical data
5 which we felt we should present to the panel had to do
6 with the infectivity studies that were performed with
7 rats. In this study, 20 animals per group were
8 treated with either nothing at all, which was called
9 the surgical control, Ringer's lactate, Hyskon or
10 INTERGEL following the implantation of fecal material
11 into the abdominal cavity.

12 A what I'm calling an LD-25 -- I think the
13 original protocol said LD-10, but since the number of
14 surgical controls that died was approximately an LD-
15 25, I'm calling it an LD-25.

16 So LD-25 and abscess formation was
17 determined. If you looked at the results, none of the
18 treatments resulted in more abscess formation than the
19 surgical control group. That's for all of the
20 treatments listed above.

21 If you look at the data on survival, the
22 surgical control was five out of 20, which is 25

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1 percent. Ringer's lactate was at five mLs per
2 kilogram and 15 mLs per kilogram, which is the
3 clinically equivalent dose and three times the
4 clinically equivalent dose.

5 We found three out of 20 in the five mL
6 and five out of 20 animals died -- I put "survival"
7 but it means number of dead animals. I'm sorry. It
8 says number of dead animals.

9 And then for Hyskon, we really don't need
10 to comment on Hyskon, but INTERGEL for five and nine
11 or for five and 15 was 25 and 45 percent.

12 The conclusion the sponsor reached in
13 their submission was that there was no statistical
14 difference between INTERGEL and Ringer's lactate, and
15 it was FDA's conclusion that the study was just not
16 powered enough to detect the 20 percent difference
17 observed as being statistically relevant.

18 So as a follow-up, FDA had asked the
19 sponsor to propose a follow-up study, and the sponsor
20 has submitted an acceptable protocol for a second
21 study which is powered to determine a 25 percent/50
22 percent mortality projected for the control versus 75

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1 percent mortality projected for INTERGEL difference in
2 an LD-50 survival study. Abscess formation will also
3 be assessed.

4 I'd like to now call on Dr. Horbowyj to
5 give FDA's clinical review.

6 DR. HORBOWYJ: Good afternoon. My name is
7 Roxi Horbowyj. I'm a general and critical care
8 surgeon working in DGRD, and I'll present the FDA
9 perspective on this clinical study, which was a study,
10 as you know of INTERGEL use during laparotomy for
11 gynecologic interventions.

12 I'll go over the aspects of the clinical
13 study, being the objective, design, the effectiveness
14 outcomes, safety outcomes, and a brief summary.

15 As you've heard, INTERGEL is a .5 percent
16 ferric hyaluronic gel. It's in an aqueous solution of
17 sodium hyaluronically cross-linked with ferric
18 chloride, and the objective of the study was to assess
19 the safety and efficacy of INTERGEL compared to
20 lactate Ringer's solution in preventing or reducing
21 adhesions in patients undergoing peritoneal cavity
22 surgery.

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1 Specifically, the target population
2 preoperatively included otherwise healthy females who
3 were 18 to 45 years old and who required laparotomy
4 for infertility, pain or irregular vaginal bleeding,
5 who were desiring to retain fertility and expecting to
6 undergo second laparoscopy at six to 12 weeks after
7 their laparotomy.

8 Preoperatively patients were excluded if
9 they were pregnant, anticoagulated, on hypoglycemic
10 therapy, undergoing tubal sterilization reversal or
11 implantation, or had undergone radio or chemotherapy
12 within the last four weeks.

13 There were also intraoperative exclusion
14 criteria, and these were if adhesions were found at
15 more than 12 of 24 anatomic sites; if there were any
16 findings of interperitoneal infection, a need for
17 opening the GI or GU tract, a need for removal of an
18 anatomic site, a need for postoperative hydrotubation
19 or intraoperative use of hemostatic agents or other
20 adhesion preventive adjuvants.

21 So the design was prospective. As you
22 heard, multi-centered, 11 sites in the U.S. and five

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1 in Europe, concurrently controlled with lactated
2 Ringer's solution. Randomization did occur
3 preoperatively. However, as I mentioned, there were
4 intraoperative exclusion criteria.

5 Masking was performed by a third party at
6 the time of application of the device for a second
7 look evaluation, and the dose was 300 cc's of the
8 device per patient, and it was not adjusted for
9 patient weight. The average weight in both continents
10 for a patient was 150 pounds.

11 Follow-up occurred at seven days for labs
12 and six to 12 weeks for postoperative laparoscopy.

13 Endpoints, as you've heard, for safety
14 were adverse events and for efficacy primarily for --
15 the primary endpoint was modified American Fertility
16 Score, and the secondary endpoints were proportion of
17 adhesions, adhesion incidence, extent, and severity.

18 This design was based on the pilot study
19 which was a prospective, randomized, lactated Ringer's
20 controlled study of 21 patients who underwent
21 laparotomy for infertility with six to 12 week follow-
22 up for second look laparoscopy.

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1 In that study, the difference between
2 INTERGEL and control second look modified AFS score
3 was 4.65. The difference between INTERGEL and control
4 modified AFS changed from baseline to second look. So
5 if you subtract for each patient their baseline score
6 from their second look score, then that difference --
7 and then subtract the INTERGELS from the controls --
8 then that difference would be 4.12.

9 In the pilot study, there were no safety
10 issues identified.

11 Just to briefly go over the American
12 Fertility Score and the modified American Fertility
13 Score, as you've heard the sponsor describe, these
14 scores address incidence, severity, and extent, and
15 similarly, they provide scores of zero through 16 and
16 a distribution of scores is the same.

17 So for any given adhesion or given site
18 with an adhesion, the adhesion can be given a score of
19 one through 16.

20 The differences between these scoring
21 systems, however, is that the AFS score was developed
22 in the 1980s and is a score that's applied to four

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1 sites: the right tube, the right ovary, the left
2 tube, and the left ovary.

3 The final AFS score for patient then is
4 the lower sum of the scores per side, for the right
5 side or the left side, and so the range of the
6 possible scores is zero to 32, whichever one was lower
7 whether it was the right side or the left side.

8 The modified AFS score, on the other hand,
9 was developed for this clinical study. It assesses up
10 to 24 scores because there are 24 sites that are
11 evaluated per patient, and then assigns one score per
12 site. In this scoring system, the final MAF score per
13 patient is the average of 24 scores, and so its range
14 is zero to 16.

15 Even sites which may not have an adhesion
16 are included, and so the denominator is usually 24.

17 In the modified AFS score, the extent of
18 adhesion was not determined for sites number five;
19 which is small bowel, number eight, which is omentum;
20 number nine, which is the right colon; number ten,
21 which is the left colon.

22 Instead there sites were assigned an

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1 extent score of moderate when determining the total
2 score.

3 Further, the clinical significance of
4 neither a single modified AFS score nor a change in
5 modified AFS score are known, and if there are
6 clinical correlations to the AFS score, at this time
7 we don't know the applicability of that outcome
8 correlation to an mAFS interpretive score.

9 Also, when you calculate the mAFS scores,
10 you find that there's overlap. For example, if you
11 calculate for an adhesion at one site, you can have
12 this range of scores, and as you calculate up to 24,
13 then you could have an mAFS score of one through 16.

14 When you plot that, you find that this
15 upper edge of blue represents the maximum scores per
16 site. This lower edge represents if you have an
17 adhesion per site. Zero, of course, would be zero.

18 So this area in blue represents -- excuse
19 me -- the possible combinations of scores that you
20 could have. For example, if you have a score of two,
21 you could be a worse case of approximately three sites
22 or a score of two could also be a patient who has 24

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1 very filmy, mild extent in severity adhesions, and
2 with just looking at the AFS score, you can't really
3 tell where you are in that.

4 But also what I wanted to point out is
5 that then the study as was conducted looked at
6 patients who were basically here, and when we assigned
7 a penalty for loss to follow-up, the penalty was the
8 very corner up there.

9 Looking at the outcomes, baseline
10 evaluations, control and investigational device
11 populations in Europe and the U.S. were clinically
12 comparable for their age, weight, and labs, as well as
13 meeting inclusion and exclusion criteria.

14 The baseline in evaluations, however, for
15 the control and investigational device study
16 populations in European and U.S. were different for
17 race. As you can see, the distributions here are
18 quite different. They're similar between the cohorts
19 within the U.S. and within Europe. However, between
20 the continents they're different. There's this 40, 50
21 percent of white patients here and 80 to 90 percent of
22 population there.

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1 Similarly, for baseline evaluation you can
2 see that the incidence, extent, severity, and mAFS
3 score -- and I include AFS score here even though it
4 wasn't part of the prospective study, but I know that
5 some people may be familiar with it, and it was in the
6 PMA. So I include it here just for reference.

7 Generally, no matter which parameter you
8 looked at, in Europe it was two to three times higher
9 than within the U.S.

10 The reason, for example, looking at
11 incidents, as you can see, then this represents the
12 U.S. and Europe cohorts broken out for treatment and
13 control. The U.S. patients had an approximately 60
14 percent incidence of patients who did not have
15 adhesions, whereas in Europe there was 20 to 30
16 percent patients who did not have adhesions at
17 baseline, and the distribution was a little bit
18 different with the patients in Europe having more
19 adhesions further down in the graph.

20 So then when you look at the way the
21 procedures were distributed, I think the incidence of
22 baseline adhesions then dictated this distribution.

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1 You had about 60 percent of patients within the U.S.
2 who had no adhesiolysis because they had no adhesions
3 to be lysed or cut, in case someone is not familiar
4 with that term, and only about 40 percent who did have
5 adhesiolysis as opposed to in Europe where you had 70
6 to 80 percent patients who had adhesiolysis and only
7 20 to 30 percent who did not.

8 At second look laparoscopy, there was some
9 loss to follow-up of patients, and that was about nine
10 patients in the U.S. INTERGEL group, three for the
11 controls, and in Europe three INTERGEL patients and
12 three controls were lost to follow-up.

13 That, in turn, then gave us an intent to
14 treat population and an evaluable population. So when
15 the data was analyzed, the intent to treat population
16 data received a -- second look data received a penalty
17 of worst score, which would be 16 per site, that
18 corner that I had pointed out to you on the chart for
19 their score, whereas the evaluable patient population
20 was just on the patient -- included only the patients
21 who completed both first and second look.

22 And I will present the results for both

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1 since we have been talking about both, and that way
2 you can see the effect of the penalty on the clinical
3 data.

4 This is just to bring up the numbers first
5 all together, showing you that in the evaluable
6 patient populations when we're talking about patients
7 who had an adhesiolysis across the continent's loss to
8 follow-up the groups are somewhat similar in number.
9 The non-adhesiolysis are not -- there is a very small
10 contribution from the European cohort.

11 Now, this slide shows then evaluable
12 patients, all patients, meaning adhesiolysis and non-
13 adhesiolysis patients, both in the U.S. and Europe.
14 The circles that are red and filled are U.S. controls.
15 Triangles are U.S. INTERGEL. Triangles are always the
16 INTERGEL group. So this is the European population.

17 And what this shows you is that the U.S.
18 patients started out here -- I'm sorry. My hands is
19 shaking -- and this is their first look, and upon
20 second look the INTERGEL patients, the triangle went
21 to the triangle here and the control patients went
22 here.

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1 In turn, the European patients started
2 pretty much out around six and ended up pretty much
3 around six as far as incidence went, and the controls
4 started out about six and a half and went to just
5 below eight.

6 I presented this on this slide with the
7 ranges as they are because this represents the whole
8 range of each scale. The maximum adhesion incidence
9 would be 24, and the mean mAFS for at most could be
10 16.

11 When you look at the population separately
12 as far as adhesiolysis or non-adhesiolysis, you find
13 again the filled are the U.S. patients. The circles
14 are the control. The triangles are the INTERGEL
15 patients. You see that in the United States we have
16 a trend for control that goes this way with increase
17 in both the score and the incidence, and with INTERGEL
18 you have an increase as well, although it is as here.

19 And, however, in Europe this actually --
20 the right most triangle was the baseline, and those
21 patients, the second look score was lower here. So
22 the trend was different. Whereas in the U.S. we went

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1 from six and a half to eight and a half. In Europe
2 they went from seven and a half to about 6.8 or so.
3 I'm just reading this off the slide.

4 The controls in Europe, however, are
5 represented this way. They had a decrease in the
6 score, but pretty much their incidence did not change
7 much.

8 When you look at the non-adhesiolysis
9 patients, you see that patients for all cohorts
10 started out pretty much the same around at zero, and
11 at second look, they are as distributed here.

12 They increase in each cohort, but the
13 trends are not necessarily the same from continent to
14 continent as in the previous side for the non-
15 adhesiolysis patients -- I mean for the adhesiolysis
16 patients.

17 Now looking so -- I'm going to be focusing
18 for now on just the U.S. patients because these
19 cohorts were, I think, large enough for us to make a
20 clinical assessment of. Even in the evaluable
21 patients, there were 90 patients, more than 90
22 patients per cohort.

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1 And so in this slide you have the blue
2 presents all patients, and then the maroon and yellow
3 is the breakout, which together gives you the blue,
4 and so the maroon are the adhesiolysis patients and
5 the yellow is the non-adhesiolysis patients.

6 And I've put the different ways of
7 assessing the different parameters for outcome
8 assessment here together just so we can look at them
9 at the same time and see the differences, and so you
10 see here this is the change in the change from
11 baseline between INTERGEL and control.

12 The difference, if you take the initial
13 scores and subtract them from the second scores and
14 then subtract the differences between the two
15 treatment type, and you see that the differences
16 between INTERGEL and control are on the order of one
17 pretty much, and that there are less than one for AMFS
18 score for the non-adhesiolysis patients, a little bit
19 more than one for the adhesiolysis patients, and about
20 one for when you combined the two.

21 The incidence parallels that well with the
22 incidence being a bit less, very little, less than

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1 half a percent really, I think, difference between
2 INTERGEL and control for the incidence or the number
3 of adhesions.

4 The extents and severity are represented
5 here. The AFS score looks different, but this, if you
6 will remember, is on a range of zero to 32, and so
7 it's -- and the number of sites that are looked at are
8 much smaller, fewer.

9 If you look at the intent to treat
10 population compared to the evaluable, which I just
11 showed you, you see that now -- and this range of the
12 Y axis suggests that control is greater than INTERGEL.
13 So control is worse; INTERGEL is better. And here it
14 would be the opposites, just for orientation there.

15 And so when you include the penalty for
16 the loss to follow-up patients, you see that the
17 effects are -- there are effects for both the -- for
18 all of the parameters that you see here, with the
19 treatment group looking worse, being above zero here
20 for several of the parameters and because there were
21 more patients lost to follow-up in that group.

22 When you look at the U.S. adhesiolysis

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1 patients for both the evaluable group and the intent
2 to treat group, and you look at adhesion types at
3 second look so that there's no difference from --
4 you're not looking at differences from baseline.
5 You're just looking at second look, but you're
6 subtracting INTERGEL form -- control from INTERGEL.
7 I'm sorry.

8 And if you look at the different types of
9 adhesions as have been presented by classification by
10 the sponsor, nothing that the de novo adhesions that
11 are presented in maroon here are actually the sum of
12 the de non adhesions at surgical sites and nonsurgical
13 sites. So this number will be driven by the sum of
14 this or determined by the sum of this, and as you look
15 there in the evaluable population, what you see is
16 that particularly for the de novo surgical site
17 adhesions and the surgical adhesions, there's almost
18 a zero difference between INTERGEL and control.

19 Where you do see a difference is in the
20 informed adhesions, and again at this level. This
21 difference in de novo is really driven here by the de
22 novo adhesions at nonsurgical sites, and I think that

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1 the trend that you see in one parameter pretty much
2 holds through proportionately through the others.

3 When you look at the intent to treat
4 population, again, the penalty seems to have affected
5 the magnitude of the outcome there.

6 If you look at the non-adhesiolysis
7 patients, again, when you look at the incidence, you
8 do not see a difference between the incidence for de
9 novo adhesions at surgical sites, and surgical site
10 adhesions. There is some difference in the reformed
11 adhesions and the de novo adhesions as summed, but
12 that's driven at -- de novo adhesions -- at surgical
13 sites. And, again, the magnitude of the difference is
14 here, about a unit of measure of one, and I didn't
15 label this because it would be a change in one here,
16 means a change in AMFS score of one or one adhesion if
17 you were discussing incidence.

18 And again, if you look at the intent to
19 treat population, you can see that the penalty for the
20 nine INTERGEL patients and the three control patients
21 in the U.S. population has an effect that looks
22 differently I thought.

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1 Addressing safety, I wanted to highlight
2 the wound evaluation that was performed in the
3 clinical trial. Data was collected on an inflammation
4 opening and infection, and as you can see this is for
5 INTERGEL and control. This is for the total
6 population. This is for your reference of breakout of
7 patients who had adhesiolysis, patients who did not
8 have adhesiolysis.

9 But focusing on the whole population here,
10 you can see that the percent inflammation was 7.8 and
11 7.1, very similar for inflammation, as well as for
12 opening, 5.9 and 5.1. Infection rates, however, for
13 INTERGEL was 3.9 percent and for control was one
14 percent, and this data does represent clean and non-
15 malignant cases, as clean contaminated and dirty cases
16 were excluded interoperatively as you saw in the
17 interoperative exclusion criteria.

18 And while malignant cases were not
19 excluded, they were not enrolled probably by chance.

20 So in summary, device use was studied in
21 this protocol for clean class, non-cancer, and
22 relatively low baseline adhesion burdened patients who

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1 are otherwise in good health. The baseline evaluation
2 differences between continents per treatment group,
3 that is, per INTERGEL and per control, are greater
4 than the differences within a continent for treatment
5 group for race, as well as baseline adhesion
6 evaluation.

7 The effectiveness outcomes for treatment
8 group are not consistent between the continents. The
9 U.S. safety outcome wound infection rate was 3.9
10 percent for INTERGEL and one percent for the control
11 group, and differences in effectiveness outcome
12 measures between the U.S., INTERGEL, and control
13 cohorts were generally about a unit of one of measure
14 or less than one.

15 And to look at this back, again, on this
16 graph, what that really means is I tried to make this
17 -- each block here is essentially a unit of measure of
18 AMFS score and adhesions. So one block here is one
19 adhesion, one score. So the area of this block really
20 represents the change that you would see here or the
21 length and height.

22 Thank you.

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1 And now Dr. Kotz, our statistician, will
2 present the statistical aspects.

3 DR. KOTZ: If you'll give me a second to
4 get set up.

5 I am Richard Kotz. I will be -- a
6 statistician in the Center for Devices and
7 Radiological Health, and I will present a statistical
8 evaluation of the effectiveness of the INTERGEL
9 solution for use in reduction of pelvic adhesions.

10 First I relate how the sponsor calculated
11 their sample size. I will then describe their
12 proposed protocol and analysis plan. Before I present
13 results as specified in their analysis plan, I will
14 discuss the differences in the sponsor's presentation
15 of the data and how I will present it.

16 Then I will briefly discuss the issue of
17 pooling, and based on my concerns about finding all
18 the data, I will present stratified results, and
19 finally I will state my conclusions.

20 The sponsor conducted a pilot study of 20
21 subjects and observed a difference of 4.0 in the
22 modified AFS score between INTERGEL and the control.

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1 INTERGEL had a much more lower mean modified AFS score
2 of 1.7 to the control group's mean score of 5.68. The
3 standard deviations were 1.4 and 2.8, respectively.

4 The sponsor expected a loss to follow-up
5 of 20 percent for INTERGEL and ten percent for the
6 control group, and thus adjusted the pilot results to
7 account for this loss to follow-up by giving these
8 subjects who were lost to follow-up a score of 16, the
9 worst possible second look score.

10 This resulted in reducing the difference
11 between the two groups or what is called the effect
12 difference to 2.1 and increasing the standard
13 deviation to about five.

14 Note that both this reduction in the mean
15 and increase in the standard deviation will greatly
16 increase the calculated sample size for the study.

17 So given an effect difference, as we said,
18 of 2.1, a standard deviation of five, a power of 80
19 percent, and the two sided alpha of .05, the sponsor
20 calculated their necessary sample size to be 180 for
21 both groups, and they rounded this up to 200 total
22 subjects.

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1 Though the sponsor didn't specify a
2 statistical hypothesis, it is implied in their sample
3 size calculation. Basically they're claiming the
4 INTERGEL subjects should have a significantly lower
5 modified AFS score than the control groups or at least
6 that's what they're trying to show.

7 Thus, the sponsor proposed a study of 200
8 U.S. subjects. They were going to concurrently enroll
9 80 European subjects. If they found the U.S. and
10 European subjects to be combinable, they were going to
11 stop the U.S. study at 120 subjects and analyze the
12 combined 200 subjects.

13 Based on preliminary results, the
14 sponsor's preliminary results, the FDA and the sponsor
15 disagreed as to the combinability of the data, and the
16 sponsor ended up enrolling the full 200 U.S. subjects.

17 At FDA's request, the sponsor proposed in
18 their protocol to present an intent to treat analysis
19 since the study was sized to take into account the
20 loss to follow-up and since it is a customary way to
21 present the results of a clinical trial.

22 In their intent to treat analysis, the

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1 sponsor proposed assigning the highest modified AFS
2 score of 16 to subjects lost to follow-up.

3 Since the patients' modified AFS scores
4 were highly skewed across treatment groups, they
5 proposed using nonparametric statistics, in
6 particular, the Wilcoxon Rank-Sum Test, to compare the
7 two treatment groups.

8 And before continuing I would just like to
9 emphasize to the panel that a statistically
10 significant or nonsignificant difference does not
11 necessarily imply a clinically significant or
12 nonsignificant difference.

13 Now, I'd like to point out some of the
14 important differences between the sponsor's earlier
15 presentation of the data analyses and the analyses
16 that I will be presenting. This data that I will be
17 presenting does come from the PMA.

18 The sponsor presented only evaluable
19 patients and did not include the loss to follow-up.
20 In contrast I will be presenting intent to treat
21 analyses which include loss to follow-up and, as
22 proposed in the analysis plan, give them the worst

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1 scores at second look.

2 You should note that there were 12
3 INTERGEL subjects lost to follow-up and four for the
4 control group.

5 All of the P values presented by the
6 sponsor earlier were for two-sided, two sampled T
7 tests or they were parametric tests, but since all of
8 the data appears to be highly skewed to the right, we
9 presented nonparametric P values; we are presenting
10 nonparametric P values using the Wilcoxon Rank-Sum
11 Test.

12 Like the sponsor, I will be presenting
13 mean baseline values before first surgery and mean
14 values for second look adjusted for adhesions unlysed
15 at baseline.

16 Since the nonparametric tests use medians,
17 tests use medians, it would be preferable to use
18 medians, but these were not available to me. All mean
19 values and P values presented in this talk, as I said,
20 were presented in the PMA amendment provided by the
21 sponsor.

22 Okay. Now I'd like to look at the results

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1 presented as prospectively proposed by the sponsor in
2 their study protocol. That is 200 U.S. subjects in an
3 intent to treat analysis using P values based on the
4 nonparametric Wilcoxon Sum Rank test or Rank-Sum test.

5 First, if you'll look at the mean modified
6 AFS scores, notice that there is very little
7 difference in baseline scores between the INTERGEL and
8 lactated Ringer's groups or the control group.

9 There is also a small difference in mean
10 modified AFS score of minus .13 in favor of INTERGEL
11 group. Notice this difference is less -- excuse me.
12 Notice this difference is less than ten percent of the
13 effective difference of 2.1 for which the trial was
14 sized.

15 When looking at the lower part of the
16 table, for incidence of adhesions, we see a similar
17 result, though this favors the control group by .2 of
18 an adhesion.

19 Oh, how do I get rid of that, Roxi? Click
20 enter?

21 (Laughter.)

22 DR. KOTZ: Okay. Thank you.

1 Notice there are no -- I wanted to go back
2 to the table. I was just going to say there are no
3 statistically significant differences.

4 Okay. A major issue has been the
5 legitimacy of combining all the data into one
6 analysis. The sponsor has attempted to justify
7 pooling all the dates together by use of an analysis
8 of covariance model.

9 To use this type of model, one needs to
10 include all the interaction terms involving the
11 covariate in the model and show they are
12 nonsignificant. The sponsor did not do this.

13 Furthermore, the data is highly skewed so
14 that the analysis of covariance model, which is a
15 parametric model, is not appropriate for this data.
16 Even if the analysis of covariance is applied to the
17 ranks of the modified AFS score instead of the actual
18 values, its use is highly questionable.

19 The sponsor also excluded the important
20 clinical strata of adhesiolysis and non-adhesiolysis
21 patients from this analysis. Note that the U.S.
22 group, the U.S. study group had a 40 percent

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1 adhesiolysis patients and the European study group had
2 74 percent adhesiolysis patients. This was earlier
3 referenced by Dr. Horbowyj.

4 Furthermore, the mean baseline modified
5 AFS scores were very different for these two groups
6 with the adhesiolysis group being 40 times higher than
7 that of the non-adhesiolysis group, as you can see
8 down at the bottom of the table. The standard
9 deviation was also a factor of ten.

10 Since it is not clear that pooling all
11 subjects together is appropriate, I will now present
12 the result stratified by continent, U.S. and Europe,
13 and by surgery type, adhesiolysis and non-
14 adhesiolysis.

15 The following two intent to treat tables
16 that I will present will give means and differences
17 for a modified AFS score and adhesions incidents at
18 both baseline and second look adjusted. Though
19 medians may have been a better summary statistic to
20 present, they were not available.

21 I would also like to point out the second
22 look scores adjusted for adhesions not lysed at

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1 baseline -- that these second look scores are adjusted
2 for adhesions not lysed at baseline and are very
3 similar to the values observed for a change from
4 baseline which was discussed earlier.

5 I will also identify those comparisons
6 which have significant P values, but this only occurs
7 in the second table of the two that we'll be looking
8 at.

9 Notice in this table for non-adhesiolysis
10 patients that there is essentially no difference in
11 baseline between the two groups in either continent or
12 either modified AFS scores or adhesion incidents. In
13 fact, I didn't bother to put the differences in this
14 chart so that we could focus on the second look
15 differences instead.

16 With respect to the second look adjusted
17 means for the non-adhesiolysis patients, notice that
18 the control group appears to do slightly better, that
19 is, they have lower scores than the INTERGEL group for
20 both subgroups, U.S. and Europe.

21 For the modified AFS score, the control
22 group is one quarter of a point lower, and in Europe

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1 the control group is one and one quarter of a point
2 lower, and for adhesions in the United States, it's
3 about half an adhesion less in the control group and
4 one and a half in the European group. None of these
5 differences were significant.

6 Now, let us turn to Table 2 for
7 adhesiolysis subjects. First notice that the baseline
8 values are one to two orders of magnitude larger than
9 for the non-adhesiolysis patients in Table 1.

10 I wish I could take you back. How do I?
11 Do I click on the down arrow? Up arrow?

12 You can just look at that first line, .02,
13 approximately .02 to .07 versus 2.01 -- 1.6 to 2.7.

14 Also, notice that in this table for
15 reasons that will become apparent, I have included the
16 differences between baseline groups. For one thing
17 the differences in the baselines between groups are
18 different, and their directions are different for the
19 two continents going -- favoring, let's see. In the
20 U.S. the INTERGEL group has higher scores, and in the
21 European group the control groups have higher scores
22 at baseline.

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1 In fact, the difference in the baseline
2 modified AFS score in the European study is
3 significant at the P level of .05, and that's that one
4 over here.

5 All differences at second look do favor
6 the INTERGEL patients, but only the modified AFS score
7 for the European patients is statistically significant
8 at the P equal .04 level, but this P value has not
9 been adjusted for a subgroup analysis.

10 When we have a large number of analyses,
11 you need to adjust your P values.

12 Furthermore, this difference in the
13 modified AFS score is minus .45, is small relative to
14 the effect different that the study was designed to
15 test of 2.1, and it is also smaller and in the same
16 direction as the difference of minus .77 we observe at
17 baseline.

18 In fact, all of the second look
19 differences are of similar size to the baseline
20 differences that we observe.

21 Finally, I'd like to reiterate that a
22 statistically significant or nonsignificant difference

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1 does not necessarily imply that there's clinically
2 significant or nonsignificant difference.

3 Therefore, in conclusion, these results
4 indicate that when analyzed according to the
5 statistical plan proposed by the sponsor, that there
6 is no statistical difference between the two groups,
7 INTERGEL and lactated Ringer's, with respect to
8 difference in modified AFS score and incidence of
9 adhesions.

10 Shall I take questions? That's it.

11 DR. KRAUSE: I was going to put up the
12 questions. Okay. These are the INTERGEL panel
13 questions which we will ask the panel to discuss.

14 Data from Europe and the United States has
15 been presented in this application in patients with
16 adhesiolysis, as well as patients without
17 adhesiolysis. When the data were compared between
18 continents, there were substantial differences in
19 distribution of baseline adhesion incidence and mAFS
20 score and race. Please discuss the poolability of the
21 data across continents and the poolability of the data
22 across surgeries with adhesiolysis and without

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1 adhesiolysis, and do this, please, from a clinical
2 point of view and also a statistical point of view.

3 The second panel question is a safety
4 question. The clinical studies presented in this
5 application include only non-cancer patients
6 undergoing procedures that would usually be classified
7 as clean. Please discuss any clinical safety concerns
8 with the use of this product in cases of any
9 classification, clean, clean contaminated,
10 contaminated, or dirty cases.

11 The third panel question has to do with
12 effectiveness. FDA 21 CFR 860.7(e)(1), for
13 determination of safety and effectiveness states,
14 "There is reasonable assurance that a device is
15 effective when it can be determined that in a
16 significant portion of the target population the use
17 of the device for its intended uses and condition of
18 use, when accompanied by adequate directions for use
19 and warnings against unsafe use, will provide
20 clinically significant results."

21 In light of that statement, does the data
22 submitted in this application support (a) the mAFS

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1 scoring system to be clinically meaningful and
2 sufficient tool for assessing the number, extent, and
3 severity of peritoneal cavity adhesions during pelvic-
4 gynecologic surgery and evaluating the effectiveness
5 of interventions for adhesions; and secondly, the
6 ability of INTERGEL adhesion barrier solution to
7 reduce the adhesion burden, number, extent, severity
8 of postoperative adhesions for the treated patients?

9 The final FDA panel question has to do
10 with the indication for use of the product. The
11 sponsor has stated that INTERGEL solution is indicated
12 for use as a single use, interperitoneal instillate
13 for reduction of adhesions following gynecologic-
14 pelvic surgery. Excuse me. It has been shown to
15 reduce the incidence, extent, and severity of post
16 surgical adhesions throughout the abdominal cavity
17 when used as an adjunct to good surgical technique
18 during laparotomy procedures.

19 Please discuss the indications for a
20 device used that may be supported by the data
21 presented in this application.

22 Thank you.

1 CHAIRMAN WHALEN: Thank you, Dr. Krause.

2 We will now have the panel deliberations
3 and comments.

4 DR. KRAUSE: We would entertain questions
5 if anyone has questions for FDA.

6 CHAIRMAN WHALEN: If anyone has questions
7 then for FDA's presentation, we'll start with that.
8 Just signal if you wish to ask.

9 Dr. DeMets.

10 DR. DeMETS: I have one point of
11 clarification for my mind with Dr. Kotz's
12 presentation, whether you looked at the results
13 according to the protocol overall or by the
14 stratification. Were you presenting means, medians or
15 what?

16 For example, you had a table that says
17 mAFS, the second look, 2.6, 2.76. What number are we
18 looking at? Means?

19 Okay. The answer is means.

20 DR. KOTZ: I'm sorry. I tried to clarify
21 that. Only means were presented in this. It was --
22 had the companies. I did not have access to medians.

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1 CHAIRMAN WHALEN: Other questions?

2 (No response.)

3 CHAIRMAN WHALEN: Very well. We now will
4 begin panel deliberations and comments, and before
5 starting upon each of the panelists having the
6 opportunity to make comments and specifically
7 addressing the FDA questions, I would like to call
8 upon two of our panel members to make specific
9 comments on this PMA application.

10 We will start with Dr. Levy who will give
11 us a clinical overview of the study and then go on to
12 Dr. DeMets who will comment on the statistics of the
13 submission.

14 Dr. Levy.

15 DR. LEVY: My comments are going to be
16 very, very brief, and that is that clinically a
17 difference to be a difference has to make a
18 difference, and whether you accept FDA's analysis of
19 the data or the sponsor's analysis of the data, when
20 we get right down to it, we are looking at a
21 difference in modified AFS score of somewhere between
22 .45 and around one.

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1 When we look at clinically significant
2 data either for fertility or for pain or certainly for
3 other things, such as small bowel obstruction related
4 to adhesions, we don't know what that means, but we do
5 know that .45 out of a total score of 16 or one out of
6 a total score of 16 is more or likely meaningless
7 clinically.

8 And I think that is our charge, is to say:
9 is there a clinically significant effect here? Is
10 there something that's going to make a difference in
11 how our patients do?

12 And in analyzing this data, whether you
13 look at it from the FDA's statistician's point of view
14 or the sponsor's statistician's point of view, the
15 delta that we're looking at in modified AFS score or
16 in AFS score or in any other way that we look at this
17 in terms of number of adhesions is a minimal
18 difference. It may be a 60 percent reduction, but
19 that's a very misleading way of looking at these data.

20 So from a clinical standpoint, I think
21 we're hard-pressed to say that this device makes a
22 difference.

1 CHAIRMAN WHALEN: Thank you.

2 Dr. DeMets.

3 DR. DeMETS: Maybe after that I don't have
4 to comment. I don't know.

5 (Laughter.)

6 DR. DeMETS: Well, I have to apologize for
7 using a low tech, but I guess it's now true that both
8 industry and the government has better resources than
9 us in academia.

10 THE REPORTER: You still have to use the
11 microphone.

12 DR. DeMETS: Yeah, that's fine. I've been
13 staring at that box all morning, fearful I'm going to
14 fall over it.

15 Well, I thank you for the opportunity to
16 comment on this protocol. I've been involved with
17 design trials for, I guess, almost 30 years, and I
18 fully appreciate the challenge the sponsor has in
19 conducting such a study, and I've worked in
20 cardiology, cancer, AIDS, a whole variety of areas,
21 including a few device trials from time to time. So
22 I fully appreciate the challenges that you took on in

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1 doing this study.

2 For the sake of time, I'm going to focus
3 my comments on three issues that came up during the
4 presentations and so forth. That is the modified AFS
5 score, the intention to treat principle, and the issue
6 of pooling, and hopefully I can motivate why I want to
7 focus my comments on that.

8 I can't comment on the clinical
9 significance of this AFS score, and I've never used
10 either the AFS score or the modified AFS score, but
11 simply to say that I think it looks to me like it's
12 sort of a ranking kind of a score, and even though
13 historically the AFS score may have been used in the
14 way that was stated, I'm not motivated or at least
15 convinced that we have anything other than an ordinal
16 scale, and so that says that sort of ranking kind of
17 analyses are probably more appropriate.

18 Second of all, because it was a score that
19 was adopted or modified, adapted for this purpose, we
20 don't really have a good sense of the validation of
21 this outcome, you know, a separate population with a
22 range of patients at various ends of the adhesion

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1 score business.

2 So I think we have to worry a bit about
3 this score even though results were presented for the
4 regular AFS score which sort of goes along in the same
5 direction. Its interpretation is, at best, difficult.

6 Now, I want to take on the intention to
7 treat principle a little bit because I don't think the
8 term was used correctly at all, intention to treat.
9 Intention to treat really says all patients, all
10 outcomes, all patients randomized and all outcomes.
11 It doesn't say those who got treatment.

12 And in this study, 303 patients were
13 randomized, 281 were enrolled that has been given
14 therapy, and 265 were evaluated at the second look.
15 So we have some slippage as we proceed through the
16 trial in the number of patients we're able to account
17 for, but why do people like me fuss about that?

18 I want to take the time just to give you
19 a couple of examples because I think it is important
20 in understanding. As I've said to my students, no
21 design can rescue -- I mean no analysis can rescue a
22 design which has some inherent problems. Even as I've

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1 said, this is a challenging study to do.

2 Ideally one would like to screen patients,
3 enroll them, do the surgery, do the eligibility check
4 and make sure this is the patient that we want to do,
5 then randomize to a treatment of the control, and do
6 all of the follow-up.

7 Now, I recognize from you in the protocol
8 that there's a little bit of logistics that may
9 prevent you from doing that. I'm sure you had many
10 discussions and thought about that, but that would be
11 the ideal because then you have all patients. You
12 know they're the ones you want to treat, and you
13 follow them.

14 What was done was screen, enroll,
15 randomize, then do surgery, and following the surgery
16 there was a randomization to the treatment or --
17 excuse me-- there was an application of the treatment
18 of control, but we lost some people. Nine were lost
19 to those who would have gotten treatment, the
20 INTERGEL, and 13 of those who would have gotten
21 control.

22 In this process there's a potential for

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1 bias, and bias is a big deal in clinical trials
2 because with enough subjects you can wipe out
3 variability and all you have left is bias. So if your
4 design is biased, then you're in trouble.

5 So there's the potential for bias. I
6 can't say from what I seen that there is bias, but
7 there's potential for bias, and it would take some
8 more digging, and I didn't have time to do that as
9 thoroughly as I like, but there's a potential for
10 worry.

11 Furthermore, so but these patients in
12 principle, according to the ITT principle, should be
13 in the analysis, should be accounted for, and since --
14 they're not.

15 And then we've already had some discussion
16 about the fact that once they were treated, among
17 those who were treated, 12 and four did not get the
18 second laparoscopy for some perhaps valid, quite valid
19 reasons.

20 But, again, that's in the challenge of the
21 design. Again, though we have a potential for bias.
22 What's critical in this piece is the blinding.

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1 If I was the surgeon and I knew, could
2 tell somehow which patients were going to get the
3 INTERGEL and which were going to get control, I may,
4 unconsciously or consciously, decide which ones I
5 might want to drop out, which ones I might want to
6 continue.

7 And we've learned this morning that there
8 was something like 200 of the surgeries which were
9 done, and a third party applied the therapy, but there
10 was 60 in which the surgeon who did the laparoscopy
11 also applied the therapy.

12 So there certainly is the potential for
13 bias at this step, and clearly there's bias or could
14 be the potential at this step.

15 If I can -- I'm losing my speech here --
16 let me present two quick examples as to why this is so
17 important, and one of them is worth your reading about
18 because it is what galvanized the ITT principle at the
19 FDA, a trial called the Anturane infarction trial was
20 a post infarct study that randomized 1,629 patients
21 and sort of declared 71 of those patients ineligible
22 because they didn't quite meet the criteria for the

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1 reasons I've listed here.

2 And so you say, well, 71 patients out of
3 1,629, and they're balanced, by the way, what kind of
4 trouble could that cause?

5 But if you look at the data, and you can't
6 find this presented this way in the literature yet,
7 but piece a couple of things together from the
8 original paper as well as a Temple publication; if you
9 took all of the patients who were randomized, all
10 comers, and followed the mortality results, you'd get
11 a P value of .2, 74 deaths to 89.

12 But if you looked at just those that were
13 eligible, 64 versus 85, that percent compares and
14 almost makes it, and in an earlier version it just
15 made it.

16 But if you looked at the ineligible, you
17 notice there's ten versus four, ten deaths in the
18 treatment, four in the control. And comparing those
19 who were in and those who were out in the placebo,
20 they're nearly identical mortality, but in those who
21 were on treatment in and out, it's the most
22 significant result in the study.

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1 This little experience, I said, is what
2 galvanized the ITT principle for most of us in
3 clinical trials, including the FDA. It's on all
4 patients, and just because you can sort of say, "These
5 weren't eligible. They didn't quite fit," you can see
6 the kind of trouble you can get in with sort of
7 retrospective or even on-the-fly assessment after
8 randomization is done.

9 Another reason for not including patients
10 is that, well, they didn't get the therapy, they
11 didn't get all of the therapy. This is one of many
12 examples I could share with you, but this is a cancer
13 trial, surgery and the years that follow post
14 mastectomy. This isn't my work. It's Carol Redmond
15 and others at the NASBP study or network, started by
16 this patient arm into those who got 85 percent of the
17 therapy, those who got 65/85, and those who got less
18 than 65.

19 And as you can see, if you take the
20 therapy, you do well. If you don't take the therapy,
21 you do poorly.

22 You can tinker with this definition of

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1 compliance or how much drug you got by changing the
2 definition, and you can scramble the order of these
3 curves, and furthermore, this is the placebo arm of
4 the study. So that how much therapy you get, how much
5 you participate, how much all of this stuff does
6 matter and can change results.

7 Two examples of why the ITT principle is
8 so important. You need to follow it from the
9 beginning of the randomization process. Anything that
10 happens after that has the potential at least for
11 creating bias.

12 Okay. So as I said, the blinding is very
13 important here, and there is some potential -- I can't
14 argue one way or the other -- but there is some
15 potential for bias.

16 The randomization was done by center,
17 which is good. I've found a comment somewhere that
18 all the numbers were used at some sites, and I don't
19 want to pursue that in great detail, but it was a
20 curiosity.

21 Now, the analysis issues, which is my
22 third point, mainly my third point. We've talked

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1 about the fact that this outcome, modified AFS score,
2 is probably more ordinal than continuous, and we have
3 been analyzing it as if it is continuous, which I
4 think is probably not the best way.

5 The issue of pooling. I probably am not
6 as enamored or concerned about the issue of pooling as
7 has been presented. When one -- we pool studies all
8 the time. We pool centers across multi-center trials.
9 We're always pooling studies, small studies to do a
10 multi-center trial. What's key is that the
11 randomization is done within the center, which is why
12 I asked the question.

13 What you worry about in pooling, there's
14 two kinds of interactions, quantitative and
15 qualitative. Quantitative says, yes, the treatment
16 response as a generic picture of some kind of score
17 maybe that modified the AFS score; what you worry
18 about or you look at it is the difference in effect,
19 change, but in the same direction, as things are
20 getting better in both places, just in a different
21 amount, or in fact, are you getting a different
22 message? In one place it's beneficial. In the other

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1 place it's harmful.

2 Now, depending on which analysis you look
3 at, maybe it's beneficial in one place and not
4 beneficial at all in the other, but clearly we pool
5 trials all the time with this kind of quantitative
6 interaction. I mean almost every multi-center trial
7 has that effect.

8 Where you want to worry is if you have
9 mixed messages and you're starting to pool those
10 because then in the average you've got nothing when,
11 in fact, it says one place for some reason or another
12 it's good and in another place it's harmful, and one
13 should try to at least find out what that's about.

14 The bottom picture is another way of
15 saying if you take a typical positive trial and plot
16 the results by center across centers, you almost would
17 surely find some centers it didn't work out the way
18 you wanted. Some centers you get very little effect
19 at all, but in most centers you're getting a positive
20 effect of varying degrees.

21 That's very typical of most drug studies,
22 biologic studies, and probably device trials. I know

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1 the least about device studies, but I'm going to guess
2 that would be true. You know, statistical theory says
3 it's almost guaranteed to be that way.

4 So we pool these studies all the time, and
5 so I'm not personally as worried about the pooling
6 issue as long as randomization was done within the
7 center because the center is the biggest difference
8 that we have. It covers all kinds of differences that
9 we can't even begin to describe and measure, but if we
10 randomize within the center, we've got balance there.

11 If we want to pool across, as long as we
12 don't have this on our hands, then I think I'm
13 interested in pooling results.

14 I wanted to comment that I distinguish
15 between subgroup analysis and stratified analysis, the
16 box on the right. I don't think this study is so big,
17 even though I'm sure the sponsor feels that it was a
18 lot of work and a lot of money; it's not that big a
19 study that we can do a whole lot of subgrouping.

20 So I'm not -- all I expect out of
21 subgrouping is that it gives us some kind of
22 consistency check. Are things moving in the same

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1 direction? And we can't start adjusting for
2 comparisons, and small numbers are dangerous for
3 subgrouping. But stratified analysis is okay.

4 What is stratified analysis? Well, it
5 says analyze within the groups you want. There was
6 the surgery type continent, and then add that together
7 in an appropriate way. I think that would be what I
8 would call a stratified analysis.

9 But subgroup analysis, I don't think this
10 study can stand that. The numbers get very thin, and
11 I'm very much of a pessimist and a skeptic about
12 subgroup analysis on moderate to small size studies.

13 Well, oh, and the final comment here is I
14 think this reduction in mAFS score is -- I worry. I
15 didn't do the mathematics, but in principal I worry
16 that that's a little artificial because the score
17 itself is artificial, and if you change the scale
18 somehow, you would get a different number even though
19 things are in a certain direction. I would not want
20 to ascribe that number to the effect of the therapy.

21 But there is a certain consistency of the
22 results across these, and I think I will stop there.

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1 Thank you.

2 CHAIRMAN WHALEN: Thank you, Dr. DeMets.

3 Our next order of business is that we will
4 consider each of the four FDA questions which Dr.
5 Krause has already read to us. Each of the questions
6 as we address them will be projected upon the screen,
7 and I will then ask to go around the table for each of
8 the panel members to comment, and obviously you may
9 pass if you desire.

10 To try to make it American, I won't start
11 with the same person or end with the same person every
12 time.

13 I will then make an attempt to to make a
14 precise but cogent summary of what the panel's sense
15 is on the answers, give the sponsor an opportunity to
16 comment upon it if they wish, and then ask the FDA if
17 that has adequately addressed the question.

18 (Pause in proceedings.)

19 CHAIRMAN WHALEN: Before we go to the
20 questions, my apologies. If the panel has any
21 questions about the two presentations that have just
22 been made, also if the sponsor has any questions or

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1 comments upon the two presentations that have just
2 been made, there's an opportunity to address those.

3 First, for the panel, is there anyone that
4 has a question or a comment to be made upon either of
5 the two presentations?

6 Yes, Dr. Davis.

7 DR. DAVIS: Yeah, I do. It's to the
8 statistics. Well, you didn't actually address this,
9 but it's a question I've had. On the shift analysis,
10 was that statistical analysis appropriately done?

11 DR. DeMETS: To the extent I had a chance
12 to review it, I mean, I think that's a good way -- I
13 mean, I think it's moving in the general direction,
14 getting better or getting worse.

15 DR. DAVIS: Yeah.

16 DR. DeMETS: And so they split it lumped
17 it, depending on which kind of tables you liked, but
18 if you looked at the lumped tables, there were tables
19 that showed that patients shifted from where they were
20 at the beginning to getting worse, and there was more
21 of that in the control group than in the INTERGEL
22 group.

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1 But I didn't have a chance to double check
2 the statistics if that's what you're asking, but I
3 think it's an idea. I had no trouble with that, if
4 you believe in the score and all of that.

5 DR. DAVIS: Yeah, I understand that. It's
6 just that that seemed to be more of a rank, an
7 analysis that --

8 DR. DeMETS: Yeah, it is a ranking.

9 DR. DAVIS: -- was appropriate for rank
10 type data.

11 DR. DeMETS: That analysis doesn't care
12 about this sign number. It just says in which
13 direction the thing is moving.

14 DR. DAVIS: Okay.

15 CHAIRMAN WHALEN: Dr. Talamini.

16 DR. TALAMINI: Dr. DeMets, you added this
17 different element for me of an earlier step regarding
18 an intention to treat. If I understand correctly, we
19 don't have the means or the ability to analyze that
20 effect because we just don't have that data on those
21 patients that dropped out at the earlier step; is that
22 correct?

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1 DR. DeMETS: I think that's correct.

2 CHAIRMAN WHALEN: Any other panel
3 questions or comments?

4 Any sponsor comments?

5 DR. diZEREGA: The sponsor had a couple of
6 questions. I'd like to begin with the concept of
7 intent to treat. The question relates to what does
8 intent to treat mean with these types of studies, and
9 the question is directed to Dr. Horbowyj in the first
10 instance.

11 And by way of orientation, because we've
12 had a lot of information, the intent to treat, as Dr.
13 DeMets referred to, began with pharmaceuticals and the
14 idea of patients. They drop out. Why? Perhaps
15 because there was a problem with the drug, and so
16 therefore, give them the worst score.

17 In this situation -- and they're called
18 lost to follow-up -- in this situation, there was only
19 one patient that was lost to follow-up that we have no
20 idea what happened to her. The other patients got
21 pregnant or had no complaints, and they're in the
22 INTERGEL population, and then there were three

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1 patients in both populations that did have complaints
2 and did not return for second look laparoscopy.

3 So my question to Dr. Horbowyj is: what
4 is the appropriate way to treat from a clinical
5 perspective patients who do not come back for a second
6 look laparoscopy when, in fact, that's the access to
7 the data in a patient who becomes pregnant or a
8 patient who had pain and now feels well and doesn't
9 come back to have another surgical procedure because
10 she feels fine?

11 What's the appropriate way to treat, to
12 deal with those patients from an analytical point of
13 view?

14 MR. DILLARD: Actually I'd like to address
15 that if that's all right.

16 CHAIRMAN WHALEN: Mr. Dillard has a
17 comment first.

18 MR. DILLARD: Yes, Jim Dillard.

19 I think that there's a number of ways you
20 can look at that, and I think what we try to do -- let
21 me try to give a little bit of a general response
22 about how we try to handle data in that kind of

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1 circumstance. Perhaps it won't be completely specific
2 to your application, but one of the things we try to
3 do is not only look at an intent to treat analysis,
4 which may be a classical intent to treat analysis and
5 may be a somewhat modified intent to treat analysis
6 because I believe that Dr. DeMets gave us some
7 information about the classical intent to treat and
8 then some other assumptions along the line that may be
9 termed an intent to treat but may not be a classical
10 one.

11 I think what we try to do is utilize not
12 only an intent to treat analysis, but an evaluable
13 patient analysis as to ways to look at data, and I
14 think sometimes you need to have a clinical look or a
15 clinical implication to one or the other of those
16 looks, and then I think you need to utilize both of
17 those in your decision about whether a product is
18 approvable or not.

19 So I would say that that's how we at FDA
20 try to use those, is try to take those as perhaps --
21 and I use these terms loosely -- but a best case and
22 a worst case analysis, perhaps believing that it's

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1 maybe somewhere in the middle, and that if there's
2 reasonable assurance of safety and effectiveness not
3 only at the ends of the spectrum, but in the middle,
4 it's a pretty good indicator that the product ought to
5 be approved.

6 And I think that's how maybe in general I
7 would characterize we use both analyses.

8 DR. diZEREGA: So then a situation in
9 adhesion prevention study whereby all of the patients
10 got pregnant with the active, which would be a
11 wonderful outcome. Even though the intent to treat
12 analysis would be a disaster, that would be the
13 favorable result based on the evaluable patient
14 consideration.

15 MR. DILLARD: Jim Dillard again.

16 Well, I would certainly make a comment
17 that if you have a clinical outcome like pregnancy,
18 that that's a far more favorable outcome in this kind
19 of circumstance than I think perhaps some of the
20 surrogates.

21 So, yes, I would say that would be a much
22 more favorable outcome.

1 DR. ROY: Could I just ask a question?
2 I'm a little confused. This morning when I asked the
3 same question, you went to great lengths to tell us
4 that you had no information, and how you're tell us
5 for the group that is lost to follow-up, namely,
6 didn't get laparoscopy, you do have the information.

7 What exactly is the message?

8 DR. diZEREGA: The question really relates
9 to what is the proper analysis for an intent to treat
10 study when the data are dependent upon a surgical
11 intervention which may become clinically unnecessary
12 due to the patient's improvement in response to the
13 first surgical procedure.

14 It's a challenge we all have with these
15 adhesion prevention studies. The classical intent to
16 treat, which we've all discussed, obviously the more
17 beneficial the device is, the larger the number of
18 patients that would not return for second look
19 evaluation and the more challenging the classical
20 intent to treat analysis would be.

21 So my question really related to what is
22 the proper way to do these types of analyses in these

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1 types of populations, and so my take home from what
2 Jim said was simply the evaluable really becomes a
3 very important part of the consideration process in
4 this situation.

5 MR. DILLARD: Can I make one comment to
6 that?

7 CHAIRMAN WHALEN: Excuse me. Mr. Dillard.

8 MR. DILLARD: Just so that I can interpret
9 my own interpretation for you, I think that from a
10 clinical perspective, and let me make the clinical
11 statement, that from the clinical perspective, and I
12 believe Dr. Horbowj outlined this, and it's why we
13 really wanted to present both the evaluable and the
14 intent to treat kind of patients is that in this case
15 and for this particular study there is a reason to
16 look at both evaluable and intent to treat because
17 there are some clinical reasons, I think, to look at
18 the evaluable patients, and there's also some protocol
19 and real statistical reasons to look at intent to
20 treat.

21 And I think that's one of the great
22 challenges that you all have before you today, is that

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1 you've got one way to look at intent to treat here
2 which statistically may very well be correct, and you
3 also have some real clinical reasons to also take a
4 look at the evaluable patient population.

5 And I think that's part of the challenge
6 we're putting to you today. So thank you.

7 CHAIRMAN WHALEN: And not to diminish the
8 importance of this particular question, but if I can
9 lend some focus upon what we're about at this
10 particular juncture, we are commenting or questioning
11 upon Dr. Levy's and Dr. DeMets' remarks. This is not
12 a particular juncture for sponsor-FDA interaction.

13 In point of fact, there is nothing in this
14 afternoon about that, although you may comment without
15 question in a few moments when we get to that
16 juncture.

17 DR. diZEREGA: Thank you.

18 Actually I misdirected the question. I
19 was actually asking the FDA, neither of the two
20 panelists. Thank you for correcting me. I forgot
21 about that.

22 But I do have a couple of questions for

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1 the panelists by way of clarification, and I
2 apologize, Dr. DeMets. I'm not a statistician, but if
3 I understand -- and basically this is a question to
4 see if I understand what you said -- in terms of these
5 types of studies with these types of data where the
6 scoring system has a very large range of numbers. The
7 absolute integral values, one to two or zero to .45,
8 may, in fact, have less meaning than changes in the
9 categorization of those patients based on the
10 tradition of the scoring system.

11 Is that a correct understanding?

12 DR. DeMETS: Well, I'm not sure I
13 understand this instrument well enough to answer your
14 question definitively, but clearly when you have an
15 instrument which assigns numbers in some arbitrary
16 fashion, the number itself to me doesn't mean as much
17 as where people fall on whatever scale you and I
18 settle on.

19 You know, you and I can go off into a
20 room, and we'd come back with a different scoring
21 system, but it may each be equally valid in ranking
22 the patients, and so we need to remember that when

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1 we're doing analysis. That was really the only point
2 I was trying to make.

3 DR. diZEREGA: I'm clear. Thank you.

4 And I guess my last question relates to
5 the term "non-adhesiolysis." In the protocol and in
6 the PMA submission, we did not consider non-
7 adhesiolysis a surgical procedure. It doesn't have a
8 CPT code and the traditional things.

9 And so when we did our analysis, we
10 considered patients with adhesiolysis and patients
11 with myomectomy, and the clinical point being that
12 many patients with myomectomy also had adhesiolysis.
13 So there's a lot of overlap between the groups.

14 My question then becomes from a clinical
15 point of view, Dr. Horbowyj, you've made comments in
16 showing how the trends and the direction was very much
17 the same. The different types of adhesions --

18 CHAIRMAN WHALEN: Excuse me. I hate to
19 interrupt, but you're addressing something to Dr.
20 Horbowyj, who is from FDA --

21 DR. diZEREGA: Oh, you're right.

22 CHAIRMAN WHALEN: -- and as I just pointed

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1 out, that's not appropriate. So if we could perhaps
2 go on to the questions at this juncture, and you'll
3 have time to comment later.

4 DR. diZEREGA: Thank you.

5 CHAIRMAN WHALEN: Thank you.

6 The first question if we can have it
7 projected before us, and again, we're going to go
8 around for panel comment, and I'll attempt to
9 summarize, briefly since Dr. Krause has already read
10 it to us has to do with the pooling of the data
11 between the U.S. and European populations, and we are
12 asked to discuss this poolability both from a clinical
13 and statistical viewpoint.

14 Dr. McCauley, do you have any comments
15 upon that?

16 DR. McCAULEY: From a clinical standpoint,
17 it's unclear to me that the data can be pooled simply
18 because of several reasons.

19 Number one relates to the patient
20 population in and of itself. Interestingly enough,
21 the mean scores were actually higher in the European
22 population even though if you go back and look at the

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1 racial distribution, you had more minorities in the
2 United States, and for someone that takes care of
3 patients that tend to have hyperproliferative scar
4 disorders, you wonder if that does translate into
5 increased adhesions in the pelvic area, particularly
6 in black patients and in patients of Hispanic descent.

7 So I do question whether or not from a
8 clinical standpoint the data is poolable.

9 From a statistical standpoint, I think
10 it's clear to me that you have to look at this in some
11 sort of nonparametric fashion rather than the data
12 that was originally presented by the sponsors. So I
13 would have severe questions as to whether or not the
14 data is poolable clinically or statistically.

15 CHAIRMAN WHALEN: Dr. Talamini.

16 DR. TALAMINI: From a clinical point of
17 view, I agree with Dr. McCauley. I'm concerned that
18 especially the baselines were different enough that
19 there were either different sets of observations based
20 upon training and experience of European surgeons or
21 differences in the patients or both and then perhaps
22 differences in the way the operations were performed,

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1 which would bring me to question whether there really
2 are insurmountable differences.

3 From a statistical point of view, I would
4 subscribe to Dr. DeMets' viewpoint that we do this all
5 the time. I'm not sophisticated enough to know if the
6 numbers are big enough to make it acceptable to do it
7 here, but I definitely agree with Dr. McCauley that it
8 seems to be a nonparametric situation with these
9 differences that we see.

10 CHAIRMAN WHALEN: Dr. DeMets, I know
11 you've been heard and paraphrased, but anything to
12 add?

13 DR. DeMETS: Probably nothing to add. I
14 think that the key thing to me is that they are
15 randomized within the center and that treatment and
16 control are balanced, and I think that's the case
17 here.

18 So that if you stratify -- I mean
19 stratify, not subgroup -- stratify your analysis
20 across sites, you've taken into account whatever
21 differences may exist between sites and between
22 continents for that matter.

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1 Whether you are interested in that
2 question is a clinical question, and so, you know,
3 that's worth perhaps a different answer, but from a
4 statistical point of view, if you balance within the
5 center by the randomization process and you don't have
6 this divergent interaction kind of thing, then I'm
7 comfortable.

8 CHAIRMAN WHALEN: Thank you.

9 Ms. Brinkman.

10 MS. BRINKMAN: I am not a statistician.

11 So I pass.

12 CHAIRMAN WHALEN: Dr. Yaross.

13 DR. YAROSS: I would agree with Dr.

14 DeMets.

15 CHAIRMAN WHALEN: Dr. Davis.

16 DR. DAVIS: I pass.

17 CHAIRMAN WHALEN: Pass after pregnant
18 pause.

19 Dr. Edmiston.

20 DR. EDMISTON: I can't add any comments to
21 what's already been mentioned.

22 CHAIRMAN WHALEN: Thank you.

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1 Dr. Levy.

2 DR. LEVY: Well, I agree with the
3 clinicians that clinically these are different groups
4 of patients. The differences that baseline scores
5 between the European and U.S. populations are greater
6 than the differences in the outcome measure with the
7 device that we're looking at.

8 So from a clinical standpoint, they're
9 different populations of patients. Statistically I
10 would have to defer to the statisticians.

11 CHAIRMAN WHALEN: And Dr. Roy.

12 DR. ROY: I'm delighted to hear the level
13 of sophistication about this statistical analysis, and
14 am gratified that it's been recommended that
15 nonparametric methods be used, as my father helped
16 develop some of them, and I don't have any problem
17 with stratification of populations from different
18 groups because by stratification, that helps give a
19 more robustness to the patient population, and I think
20 you can adjust for that within the statistical
21 analysis using the stratification technique.

22 So having said that, however, I would

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1 agree with Dr. Levy that for a difference, to make a
2 difference it should substantially show a difference,
3 and though we see a slight trend in a certain way, I'm
4 not persuaded that it would necessarily translate to
5 a difference, and I would be adverse to suggesting
6 that these arbitrary scales be translated to percent
7 change and be advertised as reducing adhesions by 60
8 percent or 80 percent or whatever.

9 So I'm very concerned with the clinical
10 applicability of this in terms of its importance.

11 CHAIRMAN WHALEN: Mr. Dillard, if I may
12 summarize, from a statistical point of view with Dr.
13 DeMets' assertion that there is randomization within
14 centers, there is not a level of concern. However,
15 the preponderance of the panel's opinion is that there
16 is clinical concern about this pooling of data.

17 Do you have any -- does that sufficiently
18 answer FDA's question?

19 MR. DILLARD: Yes, it does. Thank you.

20 CHAIRMAN WHALEN: Thank you.

21 We go on then to the second question,
22 which is the briefest of the four and is that of the

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1 oncology population of patients, as well as
2 microbiologic concerns. The question is on the
3 screen, and we'll begin the discussion with Dr.
4 Talamini.

5 DR. TALAMINI: This is a bit of a concern
6 of mine. The white count elevation that we saw in the
7 study, as well as the descriptions of infectious
8 episodes that we see in the study, in addition to some
9 of the preclinical issues give me a little bit of
10 pause for concern when you add bacteria into this mix,
11 and certainly when you add tumor cells into the mix.

12 On the other hand, this is being proposed
13 for female GYN patients without either of those
14 situations. So I think that certainly for this to be
15 broadened for more general surgical applications,
16 those would be substantial issues.

17 CHAIRMAN WHALEN: Dr. DeMets.

18 DR. DEMETS: I probably should pass, but
19 my only comment would be that I think you can only
20 apply the results of the study to the population we
21 studied and populations like it. I don't think you
22 can extrapolate beyond it.

1 CHAIRMAN WHALEN: Ms Brinkman.

2 MS. BRINKMAN: I agree, and I think it's
3 important though, as long as the clinician totally and
4 truly understands that and it's clearly marked and
5 understood that this is the only population of
6 patients to be treated and it's not used on other
7 populations of patients.

8 CHAIRMAN WHALEN: Dr. Yaross.

9 DR. YAROSS: It would seem to me that this
10 is something that can be handled in the labeling, and
11 that's typically the way issues about populations not
12 studied are handled.

13 CHAIRMAN WHALEN: Dr. Davis.

14 DR. DAVIS: I would agree that it would
15 need to be -- should not be used in the patients that
16 have these conditions if it hasn't been studied in
17 them. I have some real concerns about that.

18 CHAIRMAN WHALEN: Dr. Edmiston.

19 DR. EDMISTON: Well, I have a lot of
20 concerns. This is a relatively low risk patient
21 population, and even though we can possibly attempt to
22 control the utilization of this by a label, we know

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1 everything is used off label, and while that may not
2 be the purview of this audience, I am concerned that
3 here we are late in the game. We're still looking at
4 animal model data that hasn't come in yet.

5 So I have some great concerns relative to
6 the infectious potential of this, the fact that it is
7 coating the serosal mesothelium, the fact that the
8 sentinel macrophages that survey for contamination
9 within the peritoneal cavity might be compromised. I
10 do have some legitimate concerns.

11 CHAIRMAN WHALEN: Dr. Levy.

12 DR. LEVY: Yeah, I think our goal is first
13 do no harm. Remember this is a patient population in
14 whom the very worst thing we can do is generate
15 infection. These are people who want to preserve
16 their fertility, and the 3.9 percent infection rate
17 with the study versus one percent may not be
18 statistically significant, but it's significant enough
19 to me to raise an eyebrow and say, "What are we really
20 doing here?"

21 This is a population of patients in whom
22 we want everything to be as perfect as possible, and

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1 when we're looking at very, very small improvement in
2 adhesion scores and the possibility of any infection,
3 that does concern me.

4 CHAIRMAN WHALEN: Dr. Roy.

5 DR. ROY: I don't really have anything
6 else to add.

7 CHAIRMAN WHALEN: Thank you.

8 Dr. McCauley.

9 DR. McCAULEY: I don't have anything else
10 to add other than what's actually been said, but I am
11 a little concerned that the statistical infection
12 rate, although not significant was fourfold greater in
13 the treated patient population.

14 CHAIRMAN WHALEN: Mr. Dillard, if I may
15 summarize, there is, indeed, notably from our subject
16 expert on the panel a very significant concern about
17 infectious problems and further concern has been
18 voiced, although within the labeling which, indeed, is
19 sort of the prerequisite of what we're about here
20 there is appropriate indications for use that does not
21 focus upon this problem, but there perhaps should be
22 considerations made to admonish clinicians not to go

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1 beyond that circle.

2 Is that sufficient?

3 MR. DILLARD: Yes, it is. Thank you, Dr.
4 Whalen.

5 CHAIRMAN WHALEN: Thank you.

6 We'll now go on to question number three,
7 which starts with the determination of safety and
8 effectiveness, and in citing the Code of Federal
9 Regulations' definition, asks us to consider the data
10 as to the use of the scoring system as being
11 meaningful or otherwise, and does, indeed, the product
12 under consideration, reduce the adhesion burden.

13 Dr. DeMets, we begin with you.

14 DR. DeMETS: Well, I think that the
15 instrument that has been used -- I guess that's part
16 of the next question, but if we're talking about
17 effectiveness, I have to at least comment on it. I
18 think it is an instrument which is hard to determine
19 without further data as to how effective this is. It
20 may be on the fence statistically. One analysis says
21 it's significant. Another analysis says it's
22 marginally or not significant.

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1 To me the most compelling argument I can
2 make for this is that whatever the effect is, it has
3 some sense of consistency across other outcomes and
4 across subgroups, not perfect consistency, but at
5 least there's some consistency.

6 That sort of gives me some assurance, but
7 you don't find the definitiveness and the primary
8 outcome as stated that you would like, that I would
9 like to see.

10 I'm not saying it's not there. It's just
11 not as convincing as I thought it would be.

12 CHAIRMAN WHALEN: Ms. Brinkman.

13 MS. BRINKMAN: I'd certainly defer to Dr.
14 DeMets when it comes to the first part of the
15 question. Obviously there seems to be some clinical
16 significance, but if it's how much, I certainly could
17 not interpret.

18 CHAIRMAN WHALEN: Thank you.

19 Dr. Yaross.

20 DR. YAROSS: This area of surrogate
21 endpoints is obviously a very challenging one, and
22 certainly it's up to the clinicians to provide the

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1 recommendations to the FDA as to their view on the
2 clinical efficacy.

3 I would just remind the panel that in the
4 absence of perfect tools, we need to make sure that we
5 don't put impossible burdens on sponsors. The burden
6 in the PMA regulations is that the probable benefits
7 outweigh the probable risks. So I would just ask you
8 all to consider that ratio.

9 CHAIRMAN WHALEN: Thank you.

10 Dr. Davis.

11 DR. DAVIS: Coming into this I had great
12 concern with how the MAFS or the AFS scores were
13 analyzed because I thought it was statistically
14 inappropriate because they are ranked not a continuous
15 variable.

16 The shift analysis is to me more
17 meaningful and more persuasive. I'm still struggling
18 to determine if it is persuasive enough in my own
19 mind.

20 I'm right on the fence.

21 CHAIRMAN WHALEN: Dr. Edmiston.

22 DR. EDMISTON: Well, one of the wonderful

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1 things about coming to these panels is that I always
2 learn something every time I come here, and what I've
3 discovered from the expertise in this panel is that
4 this type of scoring system in my mind leaves much to
5 be desired, and that I am unconvinced based on the
6 presentation that there really is an effect; there is
7 an efficacy of this compound to reduce adhesions in
8 the patient population at hand.

9 Now, that's coming from an individual
10 who's a microbiologist, but has the cognizance to be
11 able to listen to both statisticians and my clinical
12 colleagues.

13 So if this is the data that's presented to
14 me, then I'm unconvinced that there is an efficacy.

15 CHAIRMAN WHALEN: Dr. Levy.

16 DR. LEVY: I think our key here, as it is
17 in many of the things that we look at is what does
18 clinical effectiveness mean, and clearly we're looking
19 at a surrogate endpoint which is number of adhesions
20 or extent of adhesions or the quality of adhesions as
21 opposed to the endpoints we'd like to be looking at,
22 which are pain, small bowel obstruction, and

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1 fertility.

2 So clearly, that being said, the sponsor
3 said that there are some studies correlating adhesions
4 with pain, correlating adhesions with fertility, but
5 there are not studies; in fact, there are other
6 studies that demonstrate a lack of correlation because
7 those variables, and there are quite a number of
8 studies that show us that the adhesions on the outside
9 of the fallopian tube are less meaningful than the
10 amount of damage to the endocell pinks (phonetic) or
11 the internal portion of the fallopian tube.

12 So I think that we need to take some of
13 those clinical correlates and throw them out the
14 window because I don't think they're very helpful to
15 us.

16 Secondly, data to support the fact that
17 reducing adhesions has any benefit with respect to
18 pain, those are very hard to come by. In fact,
19 they're nonexistent, and there are studies that show
20 us that the number of adhesions are unrelated to the
21 amount of pain that people may have.

22 So I think looking at number of adhesions

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1 as a surrogate endpoint has its own problem. Given
2 that, however, when you look at these data, even if
3 you accepted that the number and extent of adhesions
4 was an adequate endpoint to look at, I'm unconvinced
5 that these data show us a clinically significant
6 difference from the study group to the control group,
7 that a mean delta here is so small, you know, a change
8 of one compared to a total number of either 16 or 32,
9 depending on which scale you use, is not a clinically
10 significant effect of the product.

11 So I think that it's a problem using
12 number of adhesions or extent of adhesions as the
13 endpoint or as our surrogate in the first place, but
14 even if we accepted that, we still have a problem with
15 the data showing us anything that's clinically
16 effective.

17 CHAIRMAN WHALEN: Dr. Roy.

18 DR. ROY: I agree with what's been said,
19 and that's partly why I asked the question of Dr.
20 diZerega about what clinical outcome data they did
21 have with respect to pain and pregnancy, and that's
22 why I asked the second question this afternoon,

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1 because it seemed to me that he had information about
2 both of those points with respect to those patients
3 who failed to undergo second look laparoscopy.

4 And so I'm a bit perplexed. Do we or do
5 we not have data or do the sponsors have or don't have
6 data that could give us additional information so that
7 we could assess whether this change in score
8 translates to clinically meaningful outcome changes.

9 CHAIRMAN WHALEN: Dr. McCauley.

10 MR. DILLARD: Dr. Whalen, could I -- I'm
11 sorry to interject. Jim Dillard down here. Sorry.

12 Could I make one point here? Just kind of
13 a point of order from the standpoint of the FDA is
14 that one of the things that we're asking you to do is
15 to take a look at the data that's presented in the
16 PMA, and while that kind of information may be useful
17 in clarifying a decision, I think what we are asking
18 you to do here today is to try to give us some
19 feedback based on what you've seen and based on what's
20 in the application, and I think that's where we've got
21 to draw the line here today.

22 So thank you.

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1 CHAIRMAN WHALEN: Dr. McCauley, anything?

2 DR. McCAULEY: I think that regardless of
3 the scores that we achieve on these, in this
4 particular trial, there's just no data to suggest that
5 those scores translate into any clinical benefit in
6 these patients.

7 CHAIRMAN WHALEN: Dr. Talamini.

8 DR. TALAMINI: I, too, am having trouble
9 making the leap or the step from the data that we see
10 here in terms of observed numbers of adhesions to the
11 words "clinically significant results" before us or
12 the probably benefits, probably risks ratio that we're
13 talking about.

14 CHAIRMAN WHALEN: Thank you.

15 We will now project the fourth and final
16 F -- I'm sorry. First, Mr. Dillard, I have to ask you
17 if we've sufficiently answered that. I think the
18 message was clear that there is both statistical and
19 clinical concerns about the data and the
20 effectiveness.

21 MR. DILLARD: Thank you. I think we got
22 a good picture. Thank you, Dr. Whalen.

1 CHAIRMAN WHALEN: Thank you.

2 Now we go on to the fourth and final
3 question, which is the labeling as it is seen before
4 you as indications for use rather, as proposed by the
5 sponsor, and as to whether or not the panel feels that
6 the device use as stated is supported by the data that
7 has been presented in the PMA.

8 And we'll begin this one with Ms.
9 Brinkman.

10 MS. BRINKMAN: Certainly the indication
11 for you is -- I mean, our job -- my job is to
12 represent the consumer, and I think this is a product
13 that if the consumer were fully knowledgeable it
14 certainly would want to reduce adhesions, would
15 certainly want to preserve fertility. I think as a
16 consumer the consumer does not know, and so are the
17 indications for use here justifiable or are they good
18 enough?

19 And from a consumer's standpoint, I mean,
20 I'm not sure I'm really very comfortable with that,
21 and I feel that as clinicians that's certainly your
22 call, but from a consumer's standpoint, I'm not sure,

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1 and I'm not that supportive.

2 CHAIRMAN WHALEN: Thank you.

3 Dr. Yaross.

4 DR. YAROSS: I'll pass on this one.

5 CHAIRMAN WHALEN: Dr. Davis.

6 DR. DAVIS: The statement, "it has been
7 shown to reduce incidence, extent, and severity of
8 post surgical adhesions," I don't think that has been
9 demonstrated. So in looking at the data and the shift
10 data, I could see that perhaps if it was going -- a
11 woman who has a lot of adhesions, there may be some
12 benefit there, but for someone who's going in for a
13 surgery without adhesions, I don't see that the data
14 support that it's beneficial relative to the risks
15 that exist for it.

16 CHAIRMAN WHALEN: Thank you. Dr.
17 Edmiston.

18 DR. EDMISTON: I agree with Dr. Davis' two
19 points. First of all, the point that she brought out
20 is very clear. We're not convinced, at least I'm not
21 convinced that this is the case, that we have
22 demonstrated a reduction of both severity and extent.

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1 And then the other issue I just toss up is
2 that in the real world when compounds are perceived
3 either through marketing or other venues of being
4 valuable, they're used off label, and I think that's
5 a concern that has to be considered by the FDA. Will
6 this compound, will this device be used off label by
7 my surgical colleagues in general surgery, who
8 obviously see a patient population, much higher risk
9 than this study population that we've been presented
10 with?

11 CHAIRMAN WHALEN: Dr. Levy.

12 DR. LEVY: Well, I was impressed only
13 by the shift data and then only by those data in
14 patients who started out with severe adhesions, many
15 of whom or most of whom were excluded at the time of
16 surgery. In other words, the question I asked this
17 morning about patients who had greater than 11 sites
18 were excluded, which is a problem for me in analyzing
19 that shift data.

20 Secondly, the indications talk about
21 gynecologic-pelvic surgery, but indeed, that is not
22 the group of patients that were really studied here.

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1 These are patients desiring fertility who are between
2 18 and 45 years of age who wanted to preserve their
3 organs. We're not talking about hysterectomy
4 patients. We're not talking about cancer patients.
5 We're not talking, indeed, about patients when we took
6 out a tube and ovary.

7 So I think that to label it for
8 gynecologic-pelvic surgery is way too broad, even
9 assuming that we wanted to label this at all. I think
10 we'd have to limit it quite extensively. So it has to
11 be non-oncology patients, non-extirpative surgery, and
12 young patients who are desiring organ preservation.

13 And then I am, indeed, not convinced that
14 we can say that it significantly reduces adhesions.

15 CHAIRMAN WHALEN: Thank you.

16 While as chair I'm usually a talking head,
17 I have to emphasize what Dr. Edmiston has just said in
18 that I have a very deep and serious concern about the
19 wording of extent and severity of post surgical
20 adhesions throughout the abdominal cavity because,
21 indeed, above and beyond any time marketing would even
22 appear in plain English language, that would be an

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1 open invitation for general surgeons with perforated
2 diverticular, left and right, to be jumping in with
3 this stuff, and I think that that wording, just
4 focusing upon this, ignoring other issues, would need
5 to be significantly rearranged.

6 Dr. Roy.

7 DR. ROY: In addition to what's been said,
8 I think carrying forward that last thought one of the
9 concerns is that at the time of second look
10 laparoscopy wherein one was supposedly going to assess
11 the rest of the pelvis and abdomen, the small bowel,
12 et cetera, was deliberately excluded from analysis.
13 So how can you say that it is really effective
14 throughout the abdomen?

15 But getting back to the way in which the
16 data was analyzed, I was quite pleased with Dr. Kotz's
17 analysis categorizing adhesiolysis versus non-
18 adhesiolysis and finding there really substantially to
19 be no difference in the treatment or control groups,
20 and I think while it may be true that a product such
21 as this could be effective in certain stratified
22 populations, that stratified population at this point

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1 at least hasn't been identified to my satisfaction.

2 Dr. McCauley.

3 DR. McCAULEY: I have very little to add.
4 I agree with most of the comments that have been made,
5 but I would say that also in the labeling there's also
6 implied clinical benefit, not just from the standpoint
7 of adhesions. There's also implied clinical benefit
8 as you read the labeling in terms of if a patient is
9 undergoing gynecologic pelvic surgery for pain or for
10 fertility. There's implied indication that this is
11 going to improve that.

12 So I do have a problem with the labeling.

13 CHAIRMAN WHALEN: Dr. Talamini.

14 DR. TALAMINI: Nothing to add.

15 CHAIRMAN WHALEN: Dr. DeMets.

16 DR. DeMETS: Nothing to add.

17 CHAIRMAN WHALEN: Thank you.

18 Mr. Dillard, if I may attempt to
19 summarize, I believe there are serious concerns on the
20 part of the panel as to the proposed indications for
21 use both as to the data leading to the initial claim
22 as regards gynecologic-pelvic surgery, to the use of

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1 the phrase "gynecologic-pelvic surgery," and to the
2 wording of the second sentence of the indications for
3 use inasmuch as it is perhaps a subtle introduction to
4 other avenues of therapy that it would not be intended
5 for.

6 Is that adequate?

7 MR. DILLARD: Thank you, Dr. Whalen, yes.

8 CHAIRMAN WHALEN: Thank you.

9 That concludes the answering of the FDA's
10 questions. We now have a period of time, as was
11 mentioned this morning, where there can be other
12 members of the public prior to anything closing on the
13 sponsor and FDA part who wish to address us on this
14 issue.

15 If there is anyone in the audience who
16 wishes to address the panel, would you please signify
17 by raising your hand?

18 (Show of hands.)

19 CHAIRMAN WHALEN: Yes, sir. If you would
20 please come to the podium, please identify yourself,
21 your affiliations and any potential financial
22 interests in this or competing products.

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1 MR. LASSERSON (phonetic): My name is Jack
2 Lasserson, and I'm a partner at the Vertical Group.
3 It's a venture capital firm. I have an investment in
4 Lifecore, as well as in about 50 other venture based,
5 start-up medical device companies.

6 Obviously I wasn't planning to say
7 anything here today, but listening to the panel
8 discussion, and particularly to the FDA discussion,
9 has just raised tremendous concerns in my mind that
10 affect not only Lifecore, but also hundreds of other
11 start-up companies that are going before the FDA with
12 various types of applications for the approval of
13 medical devices, and I felt an obligation to kind of
14 give at least a perspective on the implications of
15 some of the suggestions that are being made here by
16 some of the panel members, as well as by the FDA.

17 One of the issues that I think we have to
18 keep in mind is that as a result of advances in
19 medical technology and the enormous amount of money
20 that has been invested in technology by the United
21 States, we have done a tremendous job of improving the
22 outcomes of patients over the last 50 years in all

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1 sorts of procedures and with all sorts of
2 pharmaceuticals.

3 The result is that we are now operating at
4 the range of 95 or 96 percent of all patients to go in
5 for a medical procedure, in general, do quite well,
6 and what we are now trying to do in, for example, the
7 people who fund the medical device industry is to move
8 it from a 96 percent good outcome to a 97 percent good
9 outcome or 98 percent good outcome. This is
10 enormously difficult.

11 You know, we're at the asymptotic point of
12 that curve. The entire presentation of the FDA today
13 was skewed by the reality that most people who have
14 surgical procedures in the hands of excellent doctors,
15 in fact, do not have adhesions. So, of course, the
16 results are going to be skewed in favor of very, very
17 small numbers relative to a very, very large potential
18 outcome.

19 As a result, the scores may tend to be
20 down in the low end of the range, and a shift at the
21 low end of the range appears to be very small because
22 relative to the entire possible range of outcomes, it

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1 is small, but relative to the patients where a change
2 matters, it's a significant change.

3 The best example of that obviously is in
4 a trial, for example, TPA for stroke where the
5 results, if you just looked at them on an absolute
6 basis, you had essentially 95 percent good outcomes.
7 The actual effect of TPA was to move mortality from I
8 think it was six or seven percent, depending on the
9 time that we were looking at, down by a percentage of
10 a half a percentage point. The absolute number was
11 extremely small.

12 In fact, the relative reduction was
13 extremely large and very beneficial, and I think
14 looking at the absolute numbers here, which is that we
15 have a fraction of a percent of a one point move
16 doesn't seem to matter, misses the larger picture of
17 the relative reduction, which is still very large.

18 This is true in almost every single trial
19 of every single device of every single company that we
20 invest in. We don't have reductions of 80 percent
21 mortality down to 20 percent or ten percent mortality.
22 Medicine is just too good for that at this point to

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