FOOD AND DRUG ADMINISTRATION

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OBSTETRICS AND GYNECOLOGY DEVICES PANEL

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SEVENTY-FIRST MEETING

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Monday, March 27, 2006

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The meeting came to order at 10:00 a.m. in the Gaithersburg Hilton, Gaithersburg, MD. Kenneth Noller, M.D., Panel Chair, presiding.

PRESENT:

Kenneth Noller, MD, Panel Chair
Paula Hillard, M.D., Voting Member
Hugh Miller, M.D., Voting Member
Jonathan Weeks, M.D., Voting Member
Marcelle I. Cedars, M.D., Voting Member
Howard Sharp, M.D., Voting Member
Diana Romero, Ph.D., Consumer Representative
Elisabeth George, Industry Representative
Scott Emerson, M.D., Ph.D., Consultant
Nasser Chegini, Ph.D., Consultant
Keith Isaacson, M.D., Consultant
Nancy Sharts-Hopko, R.N., Ph.D., Consultant
Russell Snyder, M.D., Consultant
Michael T. Bailey, Ph.D., Executive Secretary
Nancy C. Brogdon, Division Director

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

10:05 a.m.

DR. NOLLER: Good morning. I'd like to call this meeting of the Obstetrics and Gynecology Devices Panel to order. My name is Ken Noller. I'm chair of this devices panel. I'm Professor and Chair of Obstetrics and Gynecology at Tufts University and the Tufts New England Medical Center. I'm a generalist obstetrician/gynecologist by trade.

Everyone, if you haven't already signed in, please do so on the sheets that are out front. There are several different sheets depending on which category you're here as. I note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14. I'd next like to ask the panel members to each introduce themselves. I'd like to ask that you each state your name, your area of expertise, your position and affiliation. Marcelle, why don't we start with you, please?

DR. CEDARS: Marcelle Cedars, I'm a reproductive endocrinologist, I'm Division Chief of Reproductive Endocrinology and Fertility at UCSF and

Vice Chair of the Department of Obstetrics and Gynecology and Reproductive Sciences.

DR. SHARP: I'm Howard Sharp. I'm an Associate Professor of Obstetrics and Gynecology at the University of Utah. I'm a Division Director of the General Division and also the Vice Chair of the Department.

DR. HILLARD: Paula Hillard, Professor of Ob/Gyn and Pediatrics at Cincinnati Children's Hospital and Medical Center, University of Cincinnati. I do adolescent and pediatric gynecology.

DR. CHEGINI: Nasser Chegini, Professor of Ob/Gyn at the University of Florida. My area of expertise is reproductive endocrinology with emphasis in peritoneal inflammation, endometriosis and fibroids.

DR. WEEKS: Jonathan Weeks, I'm maternal fetal medicine, Norton Healthcare Systems, Director of Maternal Fetal Medicine Norton Healthcare System in Louisville, Kentucky.

DR. SHARTS-HOPKO: I'm Nancy Sharts-Hopko. My field is maternal, infant and women's health. I'm

Professor and Director of the Doctoral Program in the College of Nursing at Villanova University in Villanova, Pennsylvania.

DR. BAILEY: Mike Bailey, Food and Drug Administration. I'm the Executive Secretary of this Panel.

DR. SNYDER: I'm Russell Snyder. I'm general Ob/Gyn. I'm the Director of the Division of Gynecology at the University of Texas Medical Branch at Galveston.

DR. EMERSON: Scott Emerson, Professor of Biostatistics at the University of Washington in Seattle.

DR. ISAACSON: Keith Isaacson. I'm a Reproductive Endocrinologist and Associate Professor, Obstetrics and Gynecology at Harvard Medical School.

DR. MILLER: Hugh Miller. I'm a Maternal Fetal Medicine Specialist, Associate Professor of Ob/Gyn and Medical Director of our obstetrics practice.

DR. ROMERO: Diana Romero, Assistant Professor of Population of Family Health at Columbia

University, focusing -- research focusing primarily on women's health and reproductive and fertility related decisions.

MS. GEORGE: Elizabeth George, I'm here as the industry rep. I'm from Phillips Medical Systems and I'm the Vice President of Quality and Regulatory.

MS. BROGDON: I'm Nancy Brogdon. I'm not a member of the panel. I'm the Director of FDA's Division of Reproductive, Abdominal and Radiological Devices.

DR. NOLLER: Thank you. Next, I'd like to ask the FDA Press Contact Colin Pollard to stand up, please. If you have any questions from the press, please contact Colin. Now, we will try to run this meeting on time. We'll try to run it in an orderly fashion. We'd ask that there be no outburst from the -- from either the panel or the audience at any time. We'll do everything orderly. Everybody will have plenty of chance to ask questions and speak.

One thing I would like to ask right now, everybody make sure your cell phones are turned off, any other alarming device that you have, please shut

them off. I just checked mine. It's off. Thank you.

Next, oh, there goes one off. Next, I'll ask Mike Bailey to begin.

DR. BAILEY: All right, thanks, Dr. Noller. First, I'll start off by going to what the remainder of our tentative dates are for 2006. Our last remaining tentative dates for 2006 are June 5/6, August 28th, 29th and November 13th and 14th. I will now read into the record the deputization of temporary voting member statements and the conflict of interest statement.

First, there's two temporary voting status memos I'll read. The first one, "Pursuant to the authority granted under Medical Devices Advisory Committee Charter, dated October 27th, 1990 and amended April 20th, 1995, I appoint the following voting members of the Obstetrics and Gynecology Devices Panel for the duration of the meeting on March 27th, 2006; Russell Snyder, Nancy Sharts-Hopko, Keith Isaacson and Nasser Chegini.

For the record, these people are special

government employees and are not consultants to this panel or another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting." This was signed by Daniel Schultz, Director, Center for Devices and Radiological Health on March 14th, 2006.

The second temporary voting status memo reads, "Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health dated October 27th, 1990, and as amended August 18th, 1999, I appoint Dr. Scott Emerson to serve as a voting member of the Obstetrics and Gynecology Devices Panel for the March 27th, 2006 session of the meeting. For the record, Dr. Emerson is a member of the Reproductive Health Drugs Advisory Committee of the Center of Drug Evaluation and Research. He is a special government employee and has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting". This was signed by Jason Brodsky, Acting Associate Commissioner for the

External Relations, dated 3/14/06.

I will now read the conflict of interest statement. "The Food and Drug Administration is convening today's meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the panel are special government employees, SGEs or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this panel's compliance with federal ethics and conflict of interest laws covered by but not limited to those found in 18 USC 208 is being provided to participants in today's meeting and to the public. FDA has determined that members of this panel, including consultants, are in compliance with federal ethics and conflict of interest laws, including but not limited to 18 USC 208. Under 18 USC 208 applicable to all government agencies, Congress has

authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Members who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their employer, spouse or minor child related to discussions of today's meeting.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patent royalties, and primary employment. Today's agenda involves a review of a pre-market approval application for a post-surgical adhesion prevention device for use in patients undergoing gynecological laparoscopic surgical procedures. This is a particular matters meeting during which specific matters related to the

PMA will be discussed. Based on the agenda for today's meeting and all financial interest reported by the panel members and consultants, no conflict of interest waivers have been issued in connection with this meeting. This conflict of interest statement will be available for review at the registration table during this meeting and will be included as part of the official meeting transcript.

Ms. Elizabeth George is serving as the industry representative acting on behalf of all related industry and is employed by Phillips Medical Systems. Industry representatives do not vote. We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants need to exclude themselves from such involvement and they're exclusions will be noted for the record. FDA encourages all other participants to advise the panel of any financial relationships that they may have with the sponsor, its product and if known, its direct competitors. Thank you.

In addition, transcripts of today's meeting will be available from Neal Gross and Company. Information on purchasing videos of today's meeting can be found on the table outside the doors to the room and presenters to the panel who have not already done so, should provide FDA with a hard copy of their remarks, including overheads. Karen Oliver, Karen, will you stand, will collect these from you at the podium. Dr. Noller?

DR. NOLLER: Thank you, Mike. Colin Pollard, Chief of the Obstetrics and Gynecology Devices Branch, will have a few introductory remarks. Mr. Pollard?

MR. POLLARD: Thank you, Dr. Noller. Ladies and gentlemen of the panel, distinguished audience, good morning. First of all, I'd like to welcome you to the panel meeting held in the centennial year of FDA's existence as a regulatory body and we're very proud of that and we're happy to have you here to help us continue our legacy. I'd also like to take a moment to thank Dr. Noller. Dr. Noller was our Chairman for the last two years. Dr.

Noller has been elected President of the American College of Obstetricians and Gynecologists and will assume the role of president-elect in May. And this will, unfortunately for us, wonderful for him, be his last meeting presiding with our panel.

DR. NOLLER: Thank you.

MR. POLLARD: And we're very, very appreciative of all his great work. And now, I would like to turn to our task at hand today and that is the PMA from Innovata for its Adhesion Reduction Solution and I would just like to review a little bit of history. To date, the Center has approved three PMAs for adhesion barrier products with a gyn indication; Interceed in 1988, SepraFilm in 1996 and Intergel in 2001. None of these were approved for laparoscopic use and only Interceed and SepraFilm remain on the market at Ethicon GyneCare removed its product from the market about three years ago in response to a large number of adverse event reports.

In January of 2000 the panel met and discussed generically several key study design issues for adhesion barrier products and these discussions

led to FDA's issuance about two and a half years later of a guidance document on the type of studies FDA expects to see for adhesion barrier products. One primary take-away from that discussion was that, although we all recognize each patient is getting pelvic surgery for a specific clinical reason, it should be sufficient for a pre-market primary outcome measure to look at and properly evaluate the presence of adhesions at second laparoscopy. This, in itself, could be a clinically meaningful outcome.

The panel recognized the value of downstream clinical outcome measures, pain and fertility, small bowel obstruction, but did not believe that those must be the pre-market outcome measures. About a year and a half later, after that general discussion, in May of 2001, the panel met again, this time in a closed session, to consider the draft study design for the product before you today. The manufacturer wanted to negotiate in good faith for a study that would pass muster and FDA wanted to build on the panel discussion from the year before as well as ongoing PMA review experience suggesting that

pivotal studies needed to be better.

There were several take-aways from the discussion that day leading ultimately to the protocol employed for the pivotal study. I reviewed the transcripts recently and I thought I might share a little bit of that today with you very quickly. The panel liked the size of the study, they liked the fact that it was blinded randomization. They liked setting a minimum adhesion burden as an entry criteria. The panel commented that just counting adhesions without considering extent and severity was not going to be sufficient.

They didn't like looking for shifts from one range of adhesion counts to another, sometimes called shift table analysis but commented on the other hand, that just reducing by one adhesion, that second laparoscopy for an individual was not very compelling either. The panel emphasized the value of independent video scorers who won't know which arm a particular case is from or whether it is baseline or second laparoscopy. That panel recommended looking at the AFS score, too, and collecting the related data; age,

what kind of infertility, whether the infertility is primary or secondary, pregnancies, et cetera, and the panel commented that the market claim should be specific to what the study showed.

The panel discussion five years ago led to further adjustments of the study design into what you have before you now, with three co-primary study end points. In particular, working with us the sponsors set what was felt to be a stringent definition of patient success at the individual level and we set a mark for the minimum difference between the study and control arms and the proportion of patients who achieve this individual success. That was end point number one.

Two other measures of success were also set as co-primary end points; end point number 2, a change at the subject level at the overall number of adhesion sites. The sponsor and FDA will describe these more later. And end point number 3, a change in the number of dense adhesions. You will also hear from the results of the study. In particular, regarding end point number 1, you will hear there was

a greater proportion of patients in the study arm using Adept who met the definition of individual success but to reject for end point number 1 the study hypothesis required more than that. The lower bound on the confidence interval for this difference had to be greater than five percent and it wasn't.

For end point number 2, kind of a measure of overall adhesion burden, the study succeeded. For end point number 3, you will hear that there was no difference between the two arms for dense adhesions but the study hypothesis required the Adept arm to do better than the control. The study designed was very challenging. By statistically for the study to succeed overall, it had to succeed on three separate hypotheses for the three respective end points, and I believe the task for you today will be equally challenging, to listen carefully to the data, ask the questions you need to, and see whether or not you believe, as a panel that this product is safe and effective. That is, after taking into account how the study fared biostatistically on the three hypotheses, are the clinical findings from this study of

sufficient merit. Towards this effort, I would like to briefly review the regulatory framework we ask you to operate in when you review a PMA, in particular three definitions from our regulation.

The definitions are spelled out in a handout in your folder on the left-hand side and I'll just touch on them now. We'll go over them again in the afternoon. First of all, your decision needs to be based on valid scientific evidence and this can include well-controlled studies, partially controlled studies, studies and objective trials without match controls, well-documented case histories, and even reports of significant human history.

Safety means that the risks are outweighed by the benefits. It's as simple as that. Effectiveness means that you have seen clinically significant results and both of these measures, safety and effectiveness should be viewed through the prism of the indication for use as well as any contra-indications, warnings, precautions that are in the labeling. So that concludes my remarks, Dr. Noller, and thank you very much.

DR. NOLLER: Thank you, Mr. Pollard. We will next go to our open public hearing. At the time we put the packet together this morning, no one had registered. Is there anyone from the public that wishes to make a statement? Please raise your hand, or actually, please stand up if you do. Seeing no one, we will move onto the next section, and we'll go to the sponsor's presentation.

The sponsor has indicated that they will spend about one hour on this presentation. I would like to remind public observers at this meeting that while it is open for observation, public attendees may not participate except at the specific request of the panel. For this sponsor, the first speaker is Ms. Lorna Clisby, Director of Regulatory Affairs. Ms. Clisby, would you please introduce yourself and then if the speakers would introduce themselves as they come to the microphone. Thank you.

MS. CLISBY: Thank you. Well, good morning, everyone. My name is Lorna Clisby. I'm Director of Regulatory Affairs for Innovata, PLC. I'd like to begin by thanking the members of the panel for

giving their time to be here today and the FDA review team for giving us the opportunity to present our data on Adept Adhesion Reduction Solution for which we're seeking approval as an adjunct to adhesiolysis in gynecological laparoscopic surgery.

We have three speakers today. Professor Colin Brown is a practicing nephrologist in the UK and he has many years experience in the use of icodextrin in his patients. And he will describe to you some of the background to the development of Adept. Dr. Elizabeth Peers has had overall responsibility for the pre-clinical and clinical development of Adept and she will discuss the data from our clinical -- pivotal clinical study.

Professor Gere diZerega of the Department of Obstetrics and Gynecology School of Medicine, University of Southern California, is an expert in the field of adhesion reduction and he will speak about the clinical benefits which we see from our pivotal clinical study. We also have a number of people sitting in the audience behind me here, available to answer your questions. Two of our clinical

investigators, Dr. Anthony Luciano and Dr. Dan Martin are here. They may be known to you as past Presidents of the American Association of Gynecological Laparoscopists. Professor Steven Piantadosi is Professor of Oncology and Director of Biostatistics at Johns Hopkins University and he, together with Alison Scrimgeour, our Biostatistician, will be able to take any questions on statistics.

Professor Donald Davis, who is Professor of Toxicology at Imperial College, London, was responsible for the initial development of icodextrin and he will be able to take any questions you might have on its chemistry, toxicology, metabolism or clearance. Cathy Rogers is Research Professor in the Department of Obstetrics and Gynecology at Keck School of Medicine and she was responsible for the pre-clinical evaluation of Adept in animal models of adhesion reduction and finally, Dr. Shelagh Verco has been responsible for the management of the conduct of our clinical studies.

So I'd like to hand over to you now, Professor Brown for the first presentation.

DR. BROWN: Good morning, ladies and gentlemen of the panel. My name is Colin Brown. I'm Medical Director of Innovata, PLC. I'm also a practicing renal physician, Professor of Clinical Nephrology, University of Sheffield, Sheffield, United Kingdom. Can I have the first slide, please?

Four percent icodextrin solution is a glucose polymer. It's buffered in an electrolyte solution and isotonic to blood. Importantly in this study, it is non-viscous and it's a clear fluid. The chemistry of icodextrin is a glucose polymer which is linked at the 1/4 position. This is very important in terms of its metabolism. This makes it a dextrin and not a dextran. Dextrans are linked by the 1/6. As a result of this being a 1/4 linkage icodextrin, icodextrin is metabolized by amylase to maltose, glycerides and then to glucose.

Within the peritoneal cavity, there is no amylase, and therefore, icodextrin in this electrolyte solution, remains within the peritoneal cavity for a long period of residents time. The icodextrin being slowly absorbed because it's a large molecule and not

broken down, across the mesothelium, into the lymphatics, subsequently, into the vascular compartment where it's rapidly metabolized down to, as I said before, glycerides, maltose and glucose which is rapidly used by the normal metabolic process of the body.

In one liter there is 40 grams of carbohydrate load which is equivalent to 168 calories and as the solution is only absorbed slowly over three to four days, you can see the daily caloric load is negligible, very small. Next slide, please.

Icodextrin solution was initially developed for the purpose, I being a clinical nephrologist, for continuous peritoneal dialysis in nearly a doubling of the concentration of 7.5 percent. Not only is it double the concentration, but in peritoneal dialysis of one of the three exchanges per day, this is done to two to two and a half liters. The reason for it being a higher strength is that with people with renal failure, as you can well imagine, not only do you have to remove the waste product's metabolism, but you also need to remove fluid.

The icodextrin solution as Extraneal is for the overnight, long-term residents. Approvals for this product have been now in existence in the UK for over 10 years and more recently the United States and Japan. And as a result, there's a large body of safety experience of this product of over 75,000 patient years. Next slide, please.

This safety profile is well-established in patients with renal failure requiring dialysis and, of course, these patients are on this type of treatment daily, weekly, monthly, and many of them for many years. It is not uncommon for these patients from time to time because they have an indwelling of a peritoneal catheter, to have infection, sometimes with quite severe organisms such as pseudomonas and e-coli. There has bee no evidence in the early trial of 7.5 icodextrin that there's any increase in the infection rates when the original pivotal trial was done in the United Kingdom back in 1992.

In addition, this product is also used in those patients who have diabetes and renal failure. Some 40 to 50 percent of patients with endstage renal

failure in the United States have either Type 1 or Type 2 diabetes. And then there was a clinical observation by I and many of my other colleagues that despite these episodes of infection, where there is considerable destruction to the mesothelial layer, these patients don't appear and there's certainly no evidence in the literature, to come back with adhesion related problems such as small bowel obstruction. It was on that basis that we pursued the concept of a long residents time for fluid within the peritoneal cavity to reduce and prevent adhesions. Next slide, please.

This slide is an illustration of a -- if I can call it a clinical experiment of patients undergoing intra-peritoneal chemotherapy for colon cancer using 5-fluorouracil. These patients in between the times of having this intra-peritoneal chemotherapy, had rest periods where they weren't having their therapy and we took the opportunity with the patient's consent, as well as the IRB, to infuse into these patients over different periods of time, two liters of four percent icodextrin to get some

direct clinical evidence of how long four percent icodextrin solution remains within the peritoneal cavity. And here you will see, sorry it's a long way away, so my hand is a bit shaky as well as being a bit nervous, you can see that over four days there's still a residue within the peritoneal cavity after drainage an instillate of two liters, about half the volume that was instilled initially.

This is in comparison to crystaloid solutions. Here we have an example with saline which is rapidly absorbed over one to one and a half days and this is in keeping with literature of crystaloid reabsorption from the peritoneal cavity of between 30 and 60 mls per hour. Crucial to this long residence time is the time that it takes for adhesions to develop and this has been described in these two references and others of between naught to three days. And therefore, the concept that icodextrin solution can remain within the peritoneal cavity for a prolonged period of time is the opportunity possibly to reduce or prevent adhesion development. Next slide, please.

Well, this led to a number of pre-clinical and pilot studies and because the regulatory arrangements in Europe are different from here, we were able to obtain a European device approval in 1999. And as a result, a number of patients in Europe, both in gynecological laparoscopy and laparotomy surgery and general surgery, as the approvals were for all abdominal surgery whether laparotomy or laparoscopy, and there's over 125 patients who have received now Adept, again, another important piece of safety data that we have had to report to the agency.

Within this 125,000 patients, a registry was kept. I should say for those oncologists and clinical investigators, like myself, this wasn't a registry in terms of a huge amount of detail of information and outcome. The idea of this registry was predominantly to collect clinical evaluation, a registry called Arial Adept Registry for Clinical Evaluation, which will be outlined in a bit more detail by the agency, was published for those with gynecological laparoscopy of over 2,000 patients and

gyn surgery, which we have copies in your pack, and also an in press publication of patients undergoing general surgery.

The conclusion of the gynecological laparoscopics surgical procedure, which is this group. I quote from the paper, "Incidents of AE's reflected expected rates in gynecological surgery". Next slide.

What are the consequence of adhesions for patients? Well, they've already been outlined by Mr. Colin Pollard, of the agency, pain, not insubstantial problem, infertility, equivalent type problem and small bowel obstruction, Indeed, small bowel obstruction is the most common cause as a result of adhesions and I list a number of references below which you will have in your pack related to the slides that you've been given. And these are the consequences for patients. There's quite a large clinical burden. Next slide.

What are the consequences for surgeons? Well, obviously, and it applies to patients as well, are re-admissions of adhesion related problems as I've described in the slide before. There's additional

workload and the burden is not dissimilar to that of those patients requiring hip replacement, coronary artery by-pass graft and appendectomy. We say, I can't even get the words right, it's a different term in the United Kingdom. But more importantly, too, is the significant financial burden. This is not only to payers, those people who are having to pay the health bill for those patients who are re-admitted, but it's a significant financial burden to the patients who either lose work or intermittently can't go to work as a result of adhesion related problems.

And it was this background of this long residence time of four percent icodextrin that we embarked on our adhesion related prevention or reduction trial called Pamela pivotal trial. Next slide. Which I would like my colleague, Dr. Elizabeth Peers to go through with you in detail with relation to safety and efficacy. Thank you very much.

DR. PEERS: Good morning, ladies and gentlemen.

DR. NOLLER: Could you please speak into the microphone more directly? They're having a little

bit of trouble picking up. You need to be quite close to it unfortunately.

DR. PEERS: Good morning, ladies and gentlemen of the panel. My name is Elizabeth Peers. I'm Director of Clinical Development at Innovata, the sponsor of this clinical trial. The Adept program has been running since 1997. I've been with it since the beginning and this is a very important day for me and the rest of us on the sponsor team. Thank you, indeed, to the FDA and the panel for this opportunity. The Adept pivotal study is an unusual study in adhesion reduction. It is the largest that has taken place and it has been the only one, so far, that's been possible to have double blind.

The typing of the study you see here in the slide and that is that it was set up to determine the safety and efficacy of Adept in the reduction of adhesions after gynecological laparoscopic surgery which included adhesiolysis. Adept is a device, a medical device, which is a liquid. I have a bag here of the product which, of course, the panel is welcome to see. May I pass that round?

DR. NOLLER: Yes.

DR. PEERS: Thank you, Mr. Chairman. It's important to realize it has a two-component aspect to its use and that is that it is used as an intra-operative irrigate during surgery at least 100 mls every 30 minutes and at the end of surgery, one liter instillate is left in the peritoneal cavity before closure. May I have the next slide, please?

As I said to you, this is a double blind study, randomized and controlled. It is the highest level of robustness of clinical trial design and it's a study in adhesion reduction.

Now, double blind, what does that mean? It means that neither the patients nor the investigators nor anyone on the sponsor team nor anybody involved in statistical analysis has any idea which patients receives which device. It also means that at baseline, the two groups should be well-balanced if the randomization works so that the comparisons between groups are made on a firm foundation. Now, this was possible because Adept and Lactated Ringers appeared identical in the clinical

trial. The bag you see, which I've handed round, is not the trial bag. It is labeled with Adept and please be clear that this was not the case in the pivotal study.

LRS was our comparator. Because it's a double blind trial, clearly we had to use Ringers Lactate Solution or control in exactly the same way we used Adept. That is in the two component way of using it as an irrigant and as an instillate, so again the same fluids -- management and use of fluid for both groups in the study. I should say, however, and FDA has -- knows this too, of course, that Ringers Lactate is not approved for this use. In fact, there is no FDA approved device for adhesion reduction in laparoscopy as Mr. Pollard told us.

So to move to our study, we conducted the study entirely in the USA at 16 centers, all of which had great experience in adhesion reduction studies. Next slide, please. And here we see a list of our pivotal study investigators, the 16 listed down here for us on the left of the slide. As Ms. Clisby said, we have Dr. Luciano and Dr. Martin with us, would be

available to answer any queries you have about how they took part in this study. You will note also among this selection of eminent gynecologists, those that have been past presidents of the AAGL. Next slide, please.

Now, to move to more detail of our study design, you can see here a schematic of our study design, essentially simple. It consists of four visits for patients; a screening visit at which consent and eligibility are taken, then day zero, first surgery. This is the laparoscopic procedure for which the patient was undertaking surgery and at this point in the OR the intra-operative eligibility criteria were only available at that point and that is the point at which patients are randomized. So that is the point in the OR and at that point, there is the surgical procedure, which is recorded on video and that adhesion assessments and scoring all take place at that time in the OR.

One to three weeks later, visit three was a safety visit to follow up on any events that happened for patients since the surgical procedure and

then our final visit, visit four, is when the second laparoscopy took place and this is four to eight weeks after the initial procedure. Again, a patient assessment and scoring was conducted and that is recorded on video. I'll come back to that a little bit later on. Next slide, please.

I refer to the eligibility of patients at visit one and this slide lists the eligibility criteria, the main criteria for that and the top two are the most important. Clearly, the patient needed to be undergoing laparoscopic peritoneal surgery for a gynecological procedure which included adhesiolysis and that the patients needed to agree to a second-look four to eight weeks later. Next slide, please.

The intra-operative exclusions meant that patients could only be randomized in the OR and the top four points here show why patients -- show what patients needed to meet in order to be randomized into our study. They had to have three adhesions lysed at that time, so clearly if there were fewer than three adhesions, that patient was not eligible. Fewer than lysed that patient was not eligible. Removal of an

anatomical site meant the patient would not be eligible for our study. And finally, if all the sites could not be seen, the patient was not eligible for our study. So the randomization meant and randomization occurred at surgery in the OR with the use of device at that first point during the surgery when we knew the patient would be eligible. Next slide, please.

Here we can see a slide detailing the study enrollment. Now, up here on the left of the slide, we have the number of patients, so this tells us how many patients there were. At the end of the study we had had 777 women consent to take part in our trial. And you will note from what I've just said that they would not all be eligible and in the OR 449 patients, that's the green bar in the middle of the slide, of patients were eligible and were randomized into the study. The groups were well-balanced around 225 in each group. The randomization worked well. And this is an important group because this is the group we study for safety. All these patients were exposed to one or other medical device.

This group is also the group which we studied for our primary efficacy criteria and I will present those to you shortly. This group, the pink bar, is our per protocol group. The per protocol group followed the protocol criteria strictly and had both laparoscopies according to the protocol and this is the group we studied for our second efficacy end point which Professor diZerega will outline a little later on.

In many trials, of course, any trial, one has a withdrawal rate. You expect patients to withdraw. In this trial we expected a withdrawal rate of around 10 percent, in fact, we saw just below 7 percent, 29 patients, again, well-balanced between the groups, 15 Adept and 14 Ringers patients withdrew from the study. Before we move on, I should just outline what we have here at the bottom of this slide, and that is to note that there was a pre-specified interim review of data after half the patients were recruited, 205, and this was independent and blinded and by a data monitoring committee chaired by Professor Ed Wallach of Johns Hopkins University nearby in

Baltimore. Next slide, please.

Now, why did patients need surgery? This slide tells us the demographics and the reasons for surgery in each of our patients. Up here we have the percentage of the patients, that's not a number, it's a percentage, and across here we have the four main reasons why patients needed surgery and that were taking part in our study. And see here, pelvic pain is a primary indication for somewhere around 60 percent of the patients. Infertility was a reason for around 55 percent of patients. Known adhesive disease and known adhesions from previous medical and surgical history were known in around the same number of patients, around 55 percent. Endometriosis was a primary diagnosis in around 40 percent of patients and then a variety of other reasons, for example, myomectomy and cysectomy.

Now you can see that patients could have more than one primary diagnosis. One thing I should also say is that the red bars here, for the audience, represent the Adept group and the yellow bars represent the Ringers Lactate group. Although only 40

percent of patients have endometriosis as a primary diagnosis, in fact, around two-thirds of patients in the study had endometriosis present at the time of surgery and that's recorded in the CRF, the Case Record Forms, endometriosis, of course, associated clinically with pelvic pain and indeed, with infertility. Next slide, please.

I mentioned the double blinding of this study and one of the main purposes being to insure that the groups are well-balanced at baseline and this is, indeed, what we see. Here we have baseline adhesion assessments in the two groups; the Adept group here and the Ringers Lactate group on the right. Here we can see the incidents of adhesions in the population was around 10, just over 10, 10.3 in both the groups. Most of these adhesions were lysed, around eight and a half in each of the two groups. The extent and the severity of adhesions are also similar in the two groups. Looking further here at the number of sites with dense adhesions, again, six sites with dense adhesions in each group, most of which, 5.4, 5.2, were lysed in each of the two groups.

Moving on, we have an AFS score at baseline of just under 8, the same in each group. And the presence of endometriosis is also balanced between the two groups. So here we have a clinical picture of patients of moderate to severe burden of adhesions. They have an AFS score of just below 8. So this is patients with gynecological difficulties. So this is our patient population. Next slide, please.

When we started this study, back in 2001, as you've heard, we did not have the vast amount of safety data we now have from the European experience, both post-marketing and the from ARIEL Registry. So we were very careful to set up how we would evaluate safety in this study and the first thing I'd like to do is show you the most common -- the 10 most common adverse events that occurred between surgeries, so this is following the installation of our device, at visit 2. And you can see those data presented here.

So down here we list the top 10 most common events and here we have the Adept group and the Ringers group, the number of patients and then the percentage to give some idea of the percentage of

patients reporting. So 227 and 222 are intent to treat population here. You can see by far and away the most common event is post-procedural pain. This is no surprise as the patients have all undergone surgery. But importantly, there is no excess of pain reported in the Adept group.

Moving down, headache, always reported commonly in clinical trials in around a third of the patients. Nausea, leakage at port site, these are effectively post-procedural events reported again, at a similar rate in the two groups. Dysmenorrhea, a group of gynecological patients, no surprise at reporting similar in the two groups. Constipation and flatulence and vomiting post-procedural complications experienced by similar percentages of patients in each group. Arthralgia, again, similar in both groups. Pelvic pain, again, similar in the two groups. So those adverse events are well-balanced between the groups.

I'd like to move on now to look where there's a greater incidents of an adverse event in one or other group and that's shown for you on this slide.

So again, looking at the events that are reported between the surgeries, those were the higher incidents in one group. It's a complicated slide and I apologize to the audience if they find this difficult to see. We have here the event listed on the left as before, Adept, Ringers Lactate. This is the number of patients reporting a particular event. Over on this side we have the number of those events and we have here a column with a star, as asterisk related, and that is whether the event was considered to be related to either device in the opinion of the investigator, almost certainly, probably or possibly. So this gives us some idea of whether there's a possible relationship.

Here we can see vomiting and post-operative nausea are more common in the LRS group. However, that does not approach -- that does not achieve statistical significance and this, I should say this column down the middle is an analysis of whether that is a statistically significant difference between the groups. You can see that those are not and dysuria and pyrexia are more common in the Adept

patients, and again, those are not statistically different.

Moving down, vaginal bleeding more common in the Adept group, approaching statistical significance. These events were mostly mild to moderate and in no case considered related to either device. Diarrhea and dizziness are more common in the Lactated Ringers group, statistically significant difference there but again, considered by the investigator not to be related to either device. At the bottom here, we have an interesting event and we believe this is an event which we might expect to see in Adept patients and indeed, on some occasions in Ringers Lactate patients, vagina, vulva and labial swelling. It is reported in the literature following use of Ringers Lactate and we had seen it previously in our -- in the European use and indeed, in our feasibility studies.

And here we see reported by 13 Adept patients, six percent, and one Ringers Lactate patient, a statistically significant difference and not surprisingly either, the investigators considered

eight of those reports to be related. And I should explain a little bit about this. This was again, mostly mild to moderate and mostly occurred immediately following surgery and was mostly cleared within a few days without need for intervention or treatment. Next slide, please.

In any trial, we have to be careful to evaluate what are called serious adverse events is a regulatory definition and it usually involves a patient having to stay in the hospital for longer or to be readmitted to hospital. I should say here that there were no deaths in this study. Down here we can see the principal event for each patient who reported a serious adverse event listed down here. Here we have the Adept group. Here we have the Ringers Lactate group and right at the bottom, the total you can see that there were eight Adept patients who had serious adverse event reports and 11 Ringers Lactate patients who had serious adverse event reports. So again, no excess in the Adept group.

Here they are, abdominal or pelvic pain, similar numbers in the two groups; there were

perforations of bladder and bowel, one only in the Adept, four in the Ringers Lactate group; bleeding in vessel, two nicked vessels in the Ringers Lactate group and then illeus/constipation, one on each group, one or zero in the rest on the chart. Now, it's very difficult to make anything of this with small numbers but those appear to be well-balanced between the groups with the possible exception of the perforations and bleeding but nobody would suggest that that was in any way related to the device used.

However, there are certain patients indicated with an asterisk where the SAE was considered almost certainly probably or possibly related in the investigator's opinion. And you can see that there was one here for the Ringers Lactate group of abdominal pain; one here for Adept and pelvic pain, urinary retention was seen but considered possibly related in the Ringers Lactate group and that was also seen in the Adept group. The agency believes this event might, indeed, be related to Adept and indeed, we would support the agency in that view. Next slide, please.

Laboratory values; we measured these, the baseline visit, visit 1, and then at the safety visit between surgeries at visit 3 and then again at the second laparoscopy, visit 4. There are considerable amounts of data, as you can imagine from 449 patients measured on three occasions with around 23 different parameters. So I won't present my talk to you today but we have analyzed these data extensively. There were no differences in the mean values between the groups, Adept and Lactate Ringers. Most patients remained, as you might expect, within reference ranges, with no patterns found in shift tables, shift tables here meaning shifting from normal to abnormal or from abnormal back to normal.

Because Adept is a glucose polymer, we wanted to be able to say to you that there was no difference in blood or urine glucose levels, as Professor Brown said. The glucose load is, in fact, very small and indeed, that's what we found. No difference in blood glucose levels, no difference in urine glucose levels either. May I have the next slide, please?

So to summarize our safety data from our pivotal study, the adverse events and serious adverse events were largely related to the surgical procedure or underlying condition. There were no differences in lab values. Adept was well tolerated without an expected event of labial swelling observed in around six percent of these patients. We would expect to include indication of this in any product labeling, should that be appropriate.

So overall, the safety we've seen in this study in our 449 patients support previous safety experience with Adept, its use in Europe, as Professor Brown said, 125 patients have now -- 125,000 patients have now received this device and, indeed, some depend by our ARIEL registry where we looked at surgery of four and a half thousand patients but specifically in the group relevant to the indication we're discussing today gynecological laparoscopic surgery in 2,000, around 2,000 patients. Next slide, please.

So that concludes the safety data I'd like to present today. I'd like to move now to our primary efficacy results. Next slide, please. Just to remind

us all about what data we generated here, the adhesion assessments. So I'd like to take a little time to look again at that here. Around the peritoneal cavity there are 23 anatomical sites which we assessed for adhesions, presence or absence, that's the incidents, the extent and the severity. And those were assessed at both first and second surgery, and as I said, these procedures were videoed so we have a record of what occurred at those procedures of those occasions.

The video is important to insure that we have consistency of scoring, not only between investigators, but also over the course of the study for an individual investigator so that the way he scored at the beginning of the study was a similar way to how he scored at the end of the study. This study recruited its first patients around the summer of 2001 and the last patient left the study in around May 2004. So you can see that covered two and a half to three years. So it's a long time and we needed to insure, as I say, we had good consistency of scoring.

So what we did was we had a training of investigators and at the initial setup of the study to

make sure that scoring was done in the same way for this study. And then we had an audit procedure where a blinded video reviewer, Professor diZerega, could evaluate those scoring and make sure it retained the consistency we would expect and, indeed, for the most part, that's exactly what we observed. In cases where there was -- Professor diZerega had a different view of the scoring from the investigator, that would be resolved between the two of them and the investigator always had the final say of what that score was, so the blinded video reviewer could not influence any outcomes in this study, remembering also, of course, we had a double blind design. Next slide, please.

This is going to be virtually impossible to see from the back, but it's a copy of the case record front page for the adhesion assessments that we have from our trial and you can see -- I won't go through this in any detail but you can see that it involves considerable amounts of information being collected on adhesions, where it lies, the extent, the severity, and the presence and absence of endometriosis and whether that's treated. So a lot of

information is collected in the OR at the time of surgery. Next slide, please.

Now, to cut to the main reason I'm presenting this part of the data, there are three primary end points. Now, Mr. Pollard gave a very clear overview of the background to how we ended with the three primary endpoints we have and that was very helpful, so thank you. In summary, we do, indeed, have these three primary end points to which Colin Pollard has eluded. Our first primary end point looks at the entire group of patients, our intent to treat population, 449, and we look here for the difference between Adept and Ringers Lactate in terms of patient success. It was very clear that both the sponsor, Innovata, and the agency were very, very keen to insure that the outcomes of this study had clinical relevance. In this case, this is the first time this definition of criterion of success has been used. It is that success for an individual patient meant a decrease in adhesions of at least three sites or 30 percent of sites lysed, whichever is greater.

Adept-treated subjects -- the second

primary end point, Adept-treated subjects alone, that's the 227, we needed to insure that their burden of adhesions did not increase, that they did not have more sites with adhesions at second surgery than at first. And finally, as Mr. Pollard said, we were looking for a difference between Adept and Ringers Lactate in those patients having fewer dense adhesions at second-look than at first. Now, we need to look in more detail at the particular hypothesis for each of these three end points. Next slide, please.

So our first primary end points, the hypothesis for success again, described already what success was defined as and here we have the hypothesis that the lower bounds of the confidence interval for the difference between the two groups was above five percent. This is a stringent requirement and in fact, in a superiority study, which this is, a superiority comparison, we might normally expect, according to statistical requirements, that that's lower CI might be about zero but this is the hypothesis we have here and as Mr. Pollard said, it is a challenging one. Let us look at how that has panned out for our patients in

the data we see. Next slide, please.

So here, this is the confidence interval for the absolute difference in success. Here is the zero line, confidence interval lies tally about it and here is the five line and as we know, that confidence interval does not lie above zero. The lower bound of that confidence interval does not lie above zero. But we don't -- above five, I'm very sorry, apologies to the panel and the audience.

However, we don't conduct clinical trials entirely to look at confidence intervals. We look at what happens to the patients and that was our main driver for conducting the study and ending up with the definitions and end points we have. So let's take a look at the results in patients. Next slide, please.

Here you can see, this is our first primary end point, success, and here on the axis, we have the percentage of patients who are a success. And the red is the Adept group and the yellow, the Ringers Lactate as before, and here you can see 45 percent of Adept patients are a success. That means they all reduced by at least three adhesions and here

we have the Ringers group, again, reducing by at least three adhesions around 35 percent.

This is a statistically significant difference between the two groups, because the lower bounds of the confidence interval is above zero, as you saw on the previous slide. This is a remarkably good result for Ringers Lactate. We will be discussing that in many ways, I'm sure, later on today, but nevertheless, in adhesiolysis study, excellent investigators, good surgical technique, and optimum use of fluid, there is still an added benefit statistically significant associated with the use of Adept compared with Ringers Lactate. Next slide, please.

The second primary end point refers to the Adept group, as you know, and again, we have a statistical hypothesis here that the 95 percent 0.2 percent confidence interval for the difference should lie at less than zero, below zero for the difference between the first and second surgeries. Let us see whether that was the case. Next slide, please.

And indeed, yes, this confidence interval

lies entirely below zero and this end point was met fully. Next slide, please. To demonstrate that graphically, again, looking at patients, here we see the axis, the mean number of sites with adhesions, going up as you know, to 10, 10.3 to be precise at the first surgery, and this is reduced by 23 percent to 7.9 here at second-look surgery, highly statistically significant difference between first and second-look for Adept, so an overall reduction in incidents.

Finally, next slide, please, I'd like to look at our third end point, the hypothesis for dense adhesions and that, as Mr. Pollard said, was there should be a statistically significant difference between Adept and Ringers Lactate in the percentage of patients having fewer sites for dense adhesions at second surgery than at first. Next slide, please.

Here we can see the percentage of patients with fewer dense adhesions at the second surgery and you can see that there are 50 percent, half the patients, have a reduction. Next slide, please. However, the same is pretty much true of the Ringers Lactate group, at 49 percent. So there is no

difference between these two but remembering again in adhesiolysis study, dense adhesions are particularly challenging. They often reform and they're often difficult to lyse and might require hemostasis, but nevertheless, we see a reduction in both patient populations associated with the use of this irrigation and installation of the devices, again, a meaningful clinical result overall for the whole patient population.

So I'd like to summarize what we've found in our primary efficacy end points here. The first primary end point, we did not meet the lower bounds of the confidence interval but we had a statistically significant result. Here in the second, we have a highly statistically significant result for meeting the confidence interval requirement and the third, we have not a statistically significant result but we do have half the patients with fewer dense adhesions. Now, the statistical end points are complicated and we have Professor Steven Piantadosi here, who you may wish to ask to comment further on any of the aspects involved with the primary end points.

With that, I would like to thank the panel and the audience for the attention I've had today and I will hand over to Professor diZerega to take you through our secondary efficacy end points. Thank you.

DR. diZEREGA: Thank you very much, Dr. Peers. My name is Gere diZerega. I'm a Professor of Obstetrics and Gynecology at the University of Southern California Kecks School of Medicine in Los Angeles. In thinking about what Dr. Peers said, I think some of the members of this panel, there was a surprise. The surprise was not that the Adept did well, we expected that. The surprise was that a liter of Ringers Lactate did as well as it did. I'd like to, on the next slide, please, begin to take us through what we've learned as a result of these types of studies.

This slide lays out the available information in the literature on a volume response effect looking at the volume of a liquid that's placed in the pelvis and the ability of that liquid to separate organs long enough to reduce adhesion formation. I have taken from the literature the only

studies that are actually available, first and second-look laparoscopy of the kind of patients that were evaluated in this clinical trial and the metric that's used in commonality with all these studies is the AFS score. The AFS score is a measure of adnexal adhesions and I'll have more to say about that in just a moment. But the purpose of this slide is shown by the relationship between the top of the Lactated Ringers bars and the blue line. The blue line would indicate the level of the AFS score at the time of the first operation. And you can see when no Lactated Ringers is left in the pelvis, as is typically the case with these kinds of surgeries, there is a net increase in adhesions in the adnexal area. We've seen that time and time again in our clinical trials.

Most commonly today investigators and practitioners leave 300 milliliters in the pelvis. The reason is because 300 milliliters is the volume required to actually fill the pelvis, float the tubes and ovaries away from the side wall and the uterus and so there is the appearance of a physical separation at the time of closure and the idea being that that

physical separation will then prevent adhesions. Problem, the rapid absorption of the crystalloid outside of the pelvis, of course reduces that effect. But what we found with 1,000 milliliters which was the control use in this study, that in fact, that physical separation does exist, at least partially to the point where there is some clinical benefit, some actual reduction in measurable adhesions as shown for you on this volume response slide. What we also found is that with a longer dwell liquid in the posterior cul-de-sac of the pelvis floats the tubes and the ovaries with this pooling effect, there's an additional benefit by Adept due to its longer inter-peritoneal residence. Next slide, please.

And so what we have from the conceptual point of view is a device that has two components. The first component is used at the time of surgery and that is frequent irrigation. With frequent irrigation there is removal of the progenitors for adhesion formation, fibrin, blood clots, those types of things that inter-connect pelvic surfaces that later go on to be organized into adhesions. And as you would expect,

both Lactated Ringers and Adept had equal benefit in that situation. But following surgery as the tissues continue to undergo repair, there's an additional process of fibrin deposition and that's where we see the separation of these two devices. We have found, as have others, that adhesion formation begins somewhere around the time of surgery and continues at least through the first 36 hours post-operatively. Well, if you look at these two fluids, we can see that Lactated Ringers would be absorbed in 20 to 30 hours. This is a liter of Lactated Ringers. That would just begin to enter that 36-hour time period, so, in fact, it's not a surprise looking back that there was some benefit of this high volume fluid, and of course, with the longer inter-peritoneal residence of Adept, we would expect even further benefits and that's what I'll show you in my next slides. Slide, please.

Now, what I'm going to do is specifically address the secondary end points. Dr. Peers addressed the first end points. The secondary end points were all per protocol. That means, all of these women had both the first and second-look laparoscopy. These end

points were specified in the protocol on pages 28 and 29 and they were specified in the statistical plan on page 13, 14, 15. So these are pre-specified secondary end points, and as you can see, there are quite a number of them. We don't have time to go over all of these in detail, so what I'd like to do is show you a general overview and then begin to discuss some of them in specific. Next slide, please.

I'd like to begin by over-viewing the general trend of the secondary end points in response to these two inter-peritoneal fluids by using an odds ratio. Now, an odds ratio is a nice way to evaluate results from multiple studies or results of a study that has multiple end points. This is a display that's a familiar way to look at odds ratios. It's a very standard display, showing the results of the odds on the right-hand side. The odds ratio fundamentally is an analysis that measures the relative chance that a patient will benefit from a specific therapy, and so to do that, we've listed all the secondary end points on the left-hand portion of the slide. The line down the middle of the slide, the black line, is the

position where things separate. All the left-hand portion of the slide would show the results which favor Ringers Lactate and the right-hand portion would show results that favor Adept and the odds of an individual patient benefiting from one of these two solutions is the diamond that's wiggling around in the slide and the specific number that relates to that diamond is on the right-hand portion.

So, for example, reduction in AFS score for all the patients, 1.49 times more likely to occur -- benefit occur if the patient received Adept and so forth. And as you look across this slide, you can see that, in general, there's either a very strong benefit shown for you with a 2.72 times all the way down to a slight benefit but all the diamonds are on the right-hand portion of the slide. Now, this analysis, as you see, presented to you this morning is not adjusted for multiplicity. Indeed, there is no requirement or no pre-specification in the protocol to adjust for multiplicity and there is no need actually to adjust for multiplicity when we're just simply looking at trend analysis. And so the purpose of this slide is

just to look at the trend of these diamonds and as you can see, there's a very consistent benefit shown as all the diamonds, essentially line up far to the right-hand side of that central line. Next slide, please.

Well, let's draw our attention then to some of the specific secondary measures of outcome and let's start with de novo adhesions. And once again, the population are all the women that had a second-look laparoscopy, the protocol population. And let's measure de novo adhesions in this sense by the percent of patients that were free of de novo adhesions at the time of second-look laparoscopy. And remember with me that there were 23 different anatomical sites, any one of which could have developed an adhesion and the patient would fall out of this category. So we're talking about a very challenging end point because all the sites had to be free of de novo adhesions.

And you can see with the red bar over 50 percent of the Adept patients were free of de novo adhesions at second-look laparoscopy. The difference between the Adept patients and the control Lactated

Ringers, as you can see, is different statistically at the .029 level. Next slide, please.

Now the AFS score is a way that a number of us have been looking at adhesion outcome studies for a number of years. It was developed back in 1988 by the American Fertility Society and that's why it's called the AFS score. What the AFS score really is, is a measure of adnexal adhesions. And by adnexal adhesions we're talking about, of course, the adhesions to the tube and the ovary. They are evaluated at the time of the initial surgical procedure. If there is an adhesion on the surface, for instance, of the ovary, the extent of the ovary that's covered by that adhesion is identified and that adhesion is classified into either a filmy or a dense adhesion and then the corresponding number that would go to that categorization is shown for you here.

The scores would be added up for the right adnexa and for the left adnexa and placed into clinically meaningful categories shown for you on the next slide. The clinically meaningful categories that were established in 1988 are shown for you here, using

the numbers I outlined earlier, the minimal and mild scores between zero and 10 and the moderate and severe scores between 11 and 32. This score has been validated a number of ways. I'd like to share one of those with you on the next slide.

This is a study by Victor Gomel looking at pregnancy outcome from reconstructive surgical procedures in women with adhesions. Dr. Gomel classified the adnexa of his patients, using the ASF score, at the time that he began his reconstructive surgical procedures, into either minimal or mild categories or moderate to severe categories. And he followed the outcome, pregnancy and as you can see, almost 80 percent of the women that had minimum or mild scores at the time of the initial surgical procedure, ended up conceiving.

Conversely, if the AFS score was in the 20's, excuse me, with moderate and severe then the likelihood of the patient becoming pregnant was low and in his study about 20 percent, so it was quite predictive of the clinical result. Next slide, please.

Well, let's look at the adnexal adhesion scores for all the patients that had a second-look laparoscopy and you can see by considering a metric, a percent of patients with a reduction in AFS score between first and second-look laparoscopy of over 40 percent in the Adept group and you can see the similar comparison with the Lactated Ringers and, in fact, using all the patients in the study, this difference actually approached statistical significance. Next slide, please.

The magnitude of that reduction is shown for you on this slide. All patients in the study that underwent second-look laparoscopy there was a 35 percent reduction in the mean AFS score between first and second-look laparoscopy in Adept patients, only 15 percent in the Lactated Ringers patients, as you can see, twice the percentage and a treatment effect of some 20 percent. Next slide, please.

Now, this is a slide that takes -- that uses the adnexal adhesions score and asks a little bit of a different question and the slide is laid out a little bit differently and so let me try to take us

through this and see what it is we're trying to evaluate. The question here is, if a patient has a low adhesion burden at the time of first surgery, as categorized as minimal or mild, and that woman then undergoes a surgical procedure, as might occur with an ovarian cysectomy, simple lysis of minimal adhesions, a lot of cases that we actually do in our practices, then we want to preserve her fertility. We want her to have the ability to conceive later on if she so desires. And so the question we're asking here is how many patients had minimal to mild adhesion scores at the first operation and then continued to have minimal and mild adhesion scores at the second operation?

So in looking at the absolute numbers of women, you can see it's about 138 women at first surgery that received Adept that had very low adhesion scores. Then that number increased to 160 women at the time of second-look laparoscopy. So in this instance we're showing that the use of Adept preservers fertility and in some instances actually increases the number of patients that could become pregnant and that's where these 26 patients actually

came from, the additional 26 patients for women that had the poor scores that benefited from the use of this device. The comparator with the Lactated Ringers solution twice as many women benefited from the use of Adept who started out with low fertility -- with low minimal or mild AFS scores. Next slide, please.

I'd like to focus more specifically now on the patients who presented to this study with infertility. As Dr. Peers stated, one of the indications for surgery in our study was infertility and let's ask the question about the change in adnexal adhesion scores in this particular group of women. Well, as you can see, the percentage of patients that had a reduction in adnexal adhesions in the Adept group was actually over 50 percent. The majority of women, a little over 50 percent, actually had a reduction in adnexal adhesions with good surgical technique followed by Adept installation. That difference and compared to Ringers Lactate is 23 percent, quite a profound treatment effect, and of course, it's different statistically.

The next slide shows the magnitude of that

treatment effect once again expressed with mean AFS scores between the various groups, the infertility patients having at the time of first surgery almost an average of 10 AFS score. It went down by 34 percent at the time of second-look laparoscopy, a true reduction in AFS score and this number of 34 percent was almost three times larger than the comparator in the Lactated Ringers group and as you can see, it's statistically significant. Next slide, please.

If you look now at individual women rather than just percentages, we can see how this would turn out in a clinical situation in a very direct extrapolation. On the vertical axis now are the number of patients that presented with infertility that participated in this clinical trial and you can see it was a little over 35 that had moderate or severe adnexal adhesion scores, the presumption being that those adnexal adhesions contributed to their infertility. At the time of second-look laparoscopy, the patients that had received Adept that reduced by 16 women, quite a nice reduction, and the comparator of course, the Lactated Ringers group, there was a

reduction of only five patients, that same three times increase in benefits to individual women who have infertility and high adhesion scores at the time of reconstructive pelvic surgery. Next slide, please.

Now, what about the primary end points that this study used? How might they be applied to these analyses? I'm going to show the success criteria because it's something that does show a reduction, an absolute adhesion score and in considering the infertility population, using the success criteria defined by FDA, we've now presented on the vertical axis the percent of women that met the success criteria and you can see with the infertility population, it's essentially 50 percent of the overall patient base; of individuals who received Lactated Ringers, a 20 percent difference in success and this treatment effect of 20 percent, of course, is statistically significant. Next slide, please.

Using the same principles of analysis, the confidence interval displayed the same way. We can see that in the infertility population, who received Adept, the lower limit of the confidence interval is

well above zero which you'd expect for a superiority study, above zero and indeed, it's at 8.3 percent, quite a profound benefit by the use of Adept. Next slide, please.

Now, what about endometriosis, and the reason I'd like to pause with endometriosis is it's the most adhesiogenic disease that a woman can actually have in these types of studies. Endometriosis is very inflammatory and we would expect that if an adhesion prevention device is going to be useful to our patient population, that this would be something that would be quite a challenge for endometriosis and surgical removal of the endometriotic lesions. Over two-thirds of our patients actually ended up having endometriosis and so there were really quite a large number of patients that underwent both first and second-look laparoscopy.

Now, what I've done is I've used that same criteria of success as the metric shown for you here on the vertical axis and we've broken the patients up into different categories; one to three anatomical sites with endometriosis; four to six anatomical sites

with endometriosis and greater than six. Now, those of you that are familiar with the AFS endometriosis stage, this is different. This is looking at the number of anatomical sites that had endometriosis at the time of the first surgical procedure. And you can see casting your eye across this slide that there was a very nice treatment effect by Adept over the patients that received Lactated Ringers and it becomes even more pronounced with the more challenging condition, more than six sites with endometriosis and let me remind you, this could go all the way up to 23 anatomical sites.

The numbers of patients that we're talking about, this would actually be one of the largest studies ever with a second-look laparoscopy measuring these types of outcomes in endometriosis patients, quite a nice benefit, 25, 28 percent difference. Next slide, please.

The last patient group I'd like to address are those that we started with, namely patients undergoing adhesiolysis. So we're talking about adhesions at the first surgery and the number of

anatomical sites that were covered with adhesions or contained adhesions tells a very important story in terms of the effectiveness of an adhesion prevention device. What we've done is break out the population into the number of anatomical sites that contained adhesions into these categories and you can see the numbers of patients are very large because we're trying to include all the patients that underwent second-look laparoscopy in this analysis and with these types of planned analysis, we get a very good sense of the clinical benefit of these types of products, because, as you see, measuring success as our metric with increasing adhesion burdens, the benefit of Adept, the delta between Adept response and Lactated Ringers increases.

It's difficult to show much of benefit when the adhesion burden is low, but as the adhesion burden begins to increase, there's an increase in separation between the outcomes of success in the patients that received Adept versus Lactated Ringer solution. Next slide, please.

Well, before I conclude my remarks, I

would like to just pause for a moment and share with the panel something that's become very apparent, I think, to all of us through the day, and that is that there's an elephant in the room and by an elephant I'm talking about the difficulties that this clinical trial had with some of the primary end points. Reminding the panel that these end points were unique to this clinical trial, there was no data based on these types of end points with 1,000 milliliters of Lactated Ringers solution and Lactated Ringers did better than we thought it would do.

Having said that, I'd like to review with you what we think were the more traditional measures of clinical response in these types of studies and separate them into three different groups. The first group is Adept compared to LRS. So this is a direct comparison, similar to what you've seen throughout most of this presentation. There was, overall, a greater success rate as it's been defined, in the patients that received Adept compared to the Lactated Ringers group and of course, that number is quite different statistically. There is overall a greater

reduction in absolute numbers of adhesions as shown for you here, very important given especially the fact that the control appeared to be active. There was a greater reduction in the visceral sites with adhesions. Now, I haven't said much about visceral adhesions. Visceral adhesions are those kinds of adhesions that attach the bowel or the bladder to the anterior abdominal wall. They may not be a problem at the time of the incident surgical procedure but on subsequent surgical procedures, they often times lead to enterotomies and perforation of the bladder and so that's why we measured visceral adhesions and as you can see, there was a reduction in the instance of visceral adhesions was significant between the Adept patients versus Lactated Ringers.

The AFS score, the adnexal adhesion score, there was a greater reduction in the AFS score for the infertility patients compared to LRS and of course, more patients were free of de novo adhesions across those 23 anatomical sites in Adept compared to LRS, these numbers being quite different statistically and more infertility patients had a reduction in AFS score

in the Adept group compared to the Lactated Ringers group. The adnexal adhesion score is really showing a very nice separation between these two devices. Next slide, please.

And this is my last slide and it considers not Adept compared to LRS, it considers what happens to a patient who is going to receive Adept, what happens as we go forward with Adept available to us and our patients receive Adept, what benefits might we expect based on this large clinical trial? Well, the first is that there was a significant reduction in adhesions compared to baseline. That is to say, the patient had absolute reduction in adhesions at second-look laparoscopy which is what we're trying to do. And in addition, that significant reduction in adhesions extended to dense adhesions. Dense adhesions were also reduced compared to baseline at second-look laparoscopy.

Fifty percent of the patients, in fact, had a reduction in the sites with dense adhesions which is most -- this is actually the most profound difference that we can find in the literature with

these types of adhesion prevention devices and I think very importantly the efficacy was maintained with an increasing adhesion burden. That is to say, with increasing amounts of adhesions, the ability of Adept to reduce adhesions was not overcome throughout the entire study population, a very important observation.

Now, what about the kinds of diseases that the patients get. We've talked about adhesion counting. Let's close now with diseases or the problems that adhesions are involved with. Start with preservation of fertility. Women undergoing conservative gynecological procedures who wish to retain fertility later on, we saw that Adept benefited those patients very nicely and, indeed, in many instances, improved that potential by reduction in adnexal adhesion scores.

Endometriosis patients, a lot of data because two-thirds of the patients actually had endometriosis. There was a significant reduction in adhesions in the endometriosis patients and this difference is the largest that's ever been reported and, of course, it reached very high statistical

levels. And as the endometriosis became more extensive, as the number of anatomical sites that contained endometriosis increased, the ability to show a benefit with Adept became very clear and as -- and there was still a reduction in adhesions and at these anatomical sites irrespective of the amount of endometriosis, a unique observation.

Pain, we haven't said much about pelvic pain. It was measured in the study. There was overall an 80 percent patients that presented with pelvic pain, had a reduction of pelvic pain as it was measured at two months. I think the sponsors made a good argument about the safety record; 125,000 individuals have received Adept in a variety of surgical situations, a large number of them laparoscopic gynecologic procedures and the safety record of this particular clinical trial was as you've seen, quite remarkable.

So what we're left with then is a very high benefit to risk ratio. There was a benefit to these patients when they received Adept. There was a benefit of Adept compared to Lactated Ringers.

Patients did well overall and I think it's really a very exciting contribution to women's healthcare in the future. Thank you for your attention.

DR. NOLLER: Thank you. Panel members, this is not noted on the agenda but we will now have up to 15 minutes to ask the sponsor questions if there is something about their presentation that you did not understand, if there's something in the material that was handed out to you that you don't understand. These are really questions for clarification and we'll ask the sponsor now before lunch so they will have some time to put together the appropriate materials to answer them if they need to.

So we'll not have a dialogue with the sponsor at this point, but if you have specific questions, things you're wondering about, this is the time for us to raise them. Yes, Dr. Hillard.

DR. HILLARD: I'd like to ask a little more about the ARIEL registry and what exactly is reported in the registry and if this is voluntary reporting and the nature of what is reported.

DR. NOLLER: Thank you. Other questions?

Yes.

DR. EMERSON: I'd just like just some clarification about the blinded review of the laparoscopies in terms of whether they were blinded as to which measurements were first versus second. What sort of control there was on the laparoscopy itself which obviously, couldn't be blinded as to whether it was first or second and also -- oh, and also whether it was blinded as to the patient.

DR. NOLLER: Any other questions?

DR. DiZEREGA: I didn't understand the last point.

DR. EMERSON: The last point is, is was it known which two measurements went to the same patient by the blinded review.

DR. NOLLER: Whether it was first of second surgery?

DR. EMERSON: Well, both, whether it was the first or second but also which two went together.

DR. NOLLER: These are both Patient A.

DR. EMERSON: That's correct. Yes, Dr. Cedars.

DR. CEDARS: (Inaudible)

DR. NOLLER: No, can't hear you.

DR. CEDARS: Follow-up to that, it's my understanding and I'm not sure if this goes to Dr. Emerson's question, but the ultimate scores used for the analyses were the investigator's scores, they were not the blinded video scores. And the video was just used as a confirmatory of consistency throughout the study. Did you look at analysis including only the blinded? I mean, that would have been -- as Dr. Emerson said, that would have been the better way to do it, if you looked at did all the scoring by the video in a random fashion not knowing this was the first and this was the second, not knowing who belonged to who but graded them in a random fashion, and it's not clear that that was done.

The second question I had in your secondary analyses and when you start to break things up into groups like the infertility patients or the endometriosis patients, your group overall was very well matched because that's how they were blinded. Once you start to break into these sub-groups, we have

no evidence to tell us whether or not those subgroups were matched.

DR. DiZEREGA: At baseline.

DR. CEDARS: At baseline.

DR. NOLLER: Thank you. Dr. Weeks?

DR. WEEKS: Along the same lines, for the infertility patients, endometriosis patients, the indications for being included in the study there was quite a bit of overlap, quite a few patients had more than one indication and it's difficult in the secondary analysis, secondary end points to know how many patients had just one indication versus two or three.

DR. NOLLER: Dr. Hillard, another one?

DR. HILLARD: Just a simple clarification in terms of the adverse event of labial edema, it was stated that this was relatively short-lived. I'd like to know the range of days for resolution of the edema.

DR. NOLLER: Thank you. Yes, Dr. Isaacson.

DR. ISAACSON: Yeah, just a question on how this product was used. During the surgery, you

instilled 100 mls every 30 minutes. I assume all of that was removed at the same time. I just wanted to get that clarified. It wasn't -- none was left in. And the second question is when you leave one liter of this fluid in the abdomen is there any way to approximate how much fluid -- does it attract other body fluids in for a certain period of time? What is the volume of that and how long does that last?

DR. NOLLER: Yes, Dr. Romero?

DR. ROMERO: With regards to the reports on adverse --

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

DR. ROMERO: With regard to the data presented on the 10 common adverse events, while discussion was given with regard to absolute numbers and percents, the significance levels were not reported and it seemed like it was implied that there were no significant differences, but it's not on the slides, so I wonder if that could just be clarified.

DR. NOLLER: Dr. Miller?

DR. MILLER: Yeah, I just wanted to clarify that there was no stratification in the

randomization scheme, in other words, it was just a pure randomization. There was no stratification based on density, vascularity, extent of adhesions, so forth.

DR. NOLLER: Seeing no more questions. Some of those are relatively straightforward. Do you want to address any of them now? We have about five minutes, or do you want to wait and do it all after lunch? Please come to the podium whenever you speak.

MS. CLISBY: Lorna Clisby, Director of Regulatory Affairs. I'd like to take these questions away and answer them all in detail after lunch.

DR. NOLLER: Fine, thank you. I'm going to suggest something here that never, ever works. I'm going to suggest that we take a 10-minute break and we will be back at 10 minutes to 12:00 and the FDA will then make its presentation. Please try -- panel members, please do not speak among yourselves about these items and do not speak to the sponsor. Thank you.

(A brief recess was taken at 10:42 a.m., (On the record at 11:57 a.m.)

DR. NOLLER: Please take your seats. Our next agenda item is for the FDA to make its presentation. I'd like to ask each person who presents to identify themself and tell us which area of this you're going to speak about. First, Mr. Kuchinski, right.

MR. KUCHINSKI: That's correct.

DR. NOLLER: Good morning.

MR. KUCHINSKI: Good morning. Ladies and gentlemen, distinguished panel members and guests, I'm Michael Kuchinski, the Lead Reviewer for FDA on this pre-market approval application. I will provide a brief overview of the review process but first, I'd like to acknowledge the review team that helped me in this review. As you can see, there were a number of people who have been involved in the review of this PMA application which covered the areas of microbiology, physiology, clinical medicine, statistics and epidemiology. And included are Office of Compliance, Surveillance and Biometrics, Science and Engineering, Laboratory and Device Evaluation.

Drs. Carey-Corrado, Li and Wang will be

completing FDA's presentations today. This slide represents an outline of FDA's presentation today. I will be covering the pre-clinical review area and Dr. Carey-Corrado will be looking at the clinical summary of the PMA. Dr. Li will be looking at the statistical summary and Dr. Wang will be talking about the outside US experience, the ARIEL study and post-market expectations.

The justice for the remainder of my talk are the following and I'll be speaking about the history of the PMA, just briefly show the indications for use, a brief description of the device, although the sponsor has already presented that as well, and the pre-clinical review focus as we saw it on the PMA.

As I stated I'll be briefly describing the interactions with the company and their submission of pre-IDE for the pilot trial up to and including PMA submission. In 1999 FDA approved the IDE for the pilot investigation of Adept under the CLASSIC and RAPIDS protocols. In October 2000 the company met with FDA to discussion the pivotal clinical trial. The IDE for the pivotal trial was submitted and

approved in April 2001. Mr. Pollard already provided some background information on a closed session of the Obstetrics and Gynecology Devices Panel that was held in May of 2001 and Dr. Carey-Corrado will spend some time on that as well.

However, I will say that the company did take those discussions to heart and amended their clinical trial design in November of 2001. In May of 2004, Innovata began submitting their modular PMA submission. In the clinical module, the PMA itself was received in March of 2005. FDA requested additional information in July of 2005 and a major amendment to the file was received in December 2005.

This is the indication as proposed by the sponsor. As you can read, Adept identifies an adjunct to good surgical technique for adhesion reductions and is used during gynecological laparoscopy and it was used as an irrigant during surgery and as a post-surgical instillate. Adept is composed of glucose polymers in an isotonic solution at a concentration of four percent weight per volume. It is made up of alpha 14 glucosidic bonds and a glucose polymer

suspended in an isotonic solution consisting of sodium chloride, sodium lactate, calcium chloride, magnesium chloride and this was fractionalized but it's isolated by the fractionalization of hydrolyzed corn starch. You heard the sponsor speak about their product Extraneal which is used in peritoneal dialysis. The Extraneal product is composed of 7.5 percent icodextrin compared to Adept at four percent.

Extraneal, because of its mechanism of action was considered a drug product and was reviewed by our Center for Drug Evaluation Research. In contrast the four percent Adept icodextrin -- or excuse me, the Adept four percent icodextrin is a device because of its principal mode of action. That is, it provides a temporary physical separation of the peritoneal tissue surfaces during the early phases of the natural healing process. Because Adept is a colloid, it draws fluid from the surrounding tissue, causing a fluid reservoir to be retained in the peritoneal cavity.

This fluid reservoir is retained for up to 96 hours and may help in maintaining the tissue

separation. Adept is expected to be cleared from the peritoneal cavity by the diffusion of molecules of less than 2,000 Daltons across the peritoneal membrane and into the systemic circulation. Larger molecules will be cleared by the lymphatic system.

In the blood, icodextrin is degraded to smaller oligosaccharides by enzymatic alpha amylase, by the enzyme alpha amylase which can then be excreted in the urine and undergo -- or undergo similar further enzymatic degradation to glucose by tissue associated maltases. Now, I will go over our pre-clinical review with the PMA. The sponsor submitted validation and verification testing on the device sterility.

Shelf life data for this device has verified the shelf life of two years. These data have been reviewed and found to be acceptable to support device sterility and product shelf life. Material safety here refers to bio-compatibility testing and these tests were conducted on either Adept or Extraneal with justification and where applicable, this testing was conducted pursuant to voluntary standards, for example, the ISO, International

Standards Organization 10993, Biological Evaluations of Medical Devices. Animal testing generally refers to -- generally, our review of the animal testing focused on key testing of the device safety, including testing for delay of or prevention of healing, infectivity testing, reproductive toxicology testing, carcinogenesis, metastatic effects and the company actually provided justification for not doing these and we've accepted that justification, and pharmacokentic studies.

A detailed summary of these are presented within our Executive Summary. Nevertheless, these testings proved satisfactory to us. Your panel package also includes a number of references to the produce Extraneal, the 7.5 percent icodextrin solution for peritoneal dialysis, and since we're speaking now about manufacturing the product it was worth noting that the distributor, Baxter Healthcare, in Europe -- the European and US distributor for the Extraneal solution, conducted a voluntary recall of selected lots of Extraneal because of increasing reports of cloudy dialysate in peritoneal dialysis patients in

Europe. These episodes of aseptic -- these also included episodes of aseptic peritonitis that were attributed to contaminants of specific batches of extraneal with peptidoglycans. This high level of a bacterial contaminant were traced to one manufacturing source of Extraneal which -- of the icodextrin in Extraneal which is not used in the manufacture of Adept.

This problem has been resolved by the institution of vigorous clean processes and routine monitoring for peptidoglycans. We consider it closed. Bio-research monitoring is another thing we looked at and this is an evaluation of the study's execution, including its record keeping, compliance with informed consent and other administrative aspects of the study. Following my presentation, Dr. Carey-Corrado will discuss the clinical data, Dr. Li will be discussing the statistical approach use for analysis of the clinical data and Dr. Wang will present data collected by Innovata outside the United States, and she will also present FDA's post-market expectations for any PMA. That's it and here's Dr. Corrado.

DR. CAREY-CORRADO: Good morning, everyone. I'm going to be presenting the current status of the FDA review of the clinical data and my name is Julia Carey-Corrado as the slide says. The objectives of my presentation are to summarize marketing history, an overview to pilot studies of Adept, to discuss the design of the pivotal trial, not in great depth but to reinforce a couple of points we've made earlier about the 2001 closed panel meeting. At that point, Dr. Xuefeng Li is going to discuss in detail the FDA statistical review of the effectiveness data and then I'm going to come back to the podium very briefly to just talk about our safety review and then I'm going to be previewing the panel discussion questions because, as you all know, that's what we hope you'll spend a lot of your time this afternoon going over.

We've already heard about Extraneal which was developed and approved before Adept. Extraneal is the peritoneal dialysate and we've heard about that this morning. I don't have to go into any more detail about how it's used or the track record, but I did

want to point out that those safety issues, most common safety issues associated with Extraneal are skin reactions, usually rash and in very rare cases exfoliative dermatitis. The issue that Mike just referred to about cloudy dialysate, it is our understanding that there were about 48 complaints in European use of a cloudy dialysate. It is our understanding that the patients were asymptomatic and that the problem was based on the appearance of the fluid that was removed.

At this time, I want to talk briefly about the two pilot studies and they're important because they helped the sponsor power the pivotal clinical trial. The first pilot study was the CLASSIC study. Both of these studies were -- I'm sorry, both of these studies were prospective randomized. They were both open label, multi-center and controlled. They procedure was laparoscopic gynecological surgery. A liter of Adept was used in the test group in the CLASSIC study and approximately a liter of Lactated Ringers and the two groups were relatively well-balanced in terms of numbers.

As a digression, Lactated Ringers as a control group, we want to make it clear that this is off-label use of Lactated Ringer solution. The effectiveness has not been demonstrated for adhesion prevention for Lactated Ringers solution and of course, it is not FDA approved for that use. It is rapidly resorbed and practically we have found -- concluded that it's visually undistinguishable from Adept. This facilitates blinding although these two pilot studies were not blinded studies.

In the CLASSIC study there were two adverse events of labial or vulvar edema for a rate in the small study of 5.8 percent and all we can say about effectiveness is that the Adept patients had an observed reduction in adhesion number, extent and severity. So we can't draw too many conclusions from such a small study.

The sponsor also conducted what was called the RAPIDS study, and this similar in design except that it was a two to one randomization of Adept to Lactated Ringers and the other difference between RAPIDS from CLASSIC was that this study used a larger

volume of the test solutions. The reason for this was that the company wanted to get a feel for whether or not there would be a problem with the larger volume because they believe it should be used as an irrigant and an instillate. So if you irrigate repeatedly through a two or two and a half hour procedure and you don't remove your irrigant, then you could end up conceivably with a larger volume than 1,000 cc's when you close the patient and send her to recovery.

So that was the purpose of testing this other pilot group. There was one case of dyspnea associated with abdominal distension, one out of 25 Adept patients, and one out of 25 Adept patients also developed the vulvar edema adverse event that we have heard about already and those were what we thought to be device related based on our review. There were other complaints of bloating and distension, oozing from the incision as we would expect from this type of use.

With respect to effectiveness, again, we can't really say much except there was an observed reduction in the number, extent and severity in the

Adept subjects but there weren't any huge differences in the two groups and I'll let the company address that if they want to.

So at this time, I'm just going to say a couple more words about the panel discussion in 2001. This was a closed discussion because the company was talking about their pivotal trial design and when we had that meeting, we had -- FDA had conditionally approved the protocol for the pivotal trial but we had some uncertainty about the primary end points and we really wanted the panel to get a chance to weigh in on the primary end points for the study.

The panel, as Colin Pollard said earlier, agreed that adhesion scores were acceptable surrogates for more clinical end points like bowel obstruction and fertility, so that moving forward with adhesion scores was acceptable. The company at that time had wanted to do a shift table analysis for the incidence of sites with adhesions and the panel said that was fine but that that was not going to be sufficient. The panel was very clear that they thought that adhesion extent and severity were very important in a

trial of an adhesion prevention device and they also recommended that AFS scores also be included as end points because there was some clinical validation for AFS scoring. The problem with making the AFS score a primary end point was that neither of the pilot studies had collected the AFS data with the idea of powering the pivotal study to look at those scores. So that was one problem with using AFS scores as one of the primary end points and again, I defer to the company to address that further.

We explicitly asked the panel to talk about whether fertility evaluation was reasonable or feasible and they said that it was acceptable to look at fertility post-market depending on how the pivotal trial worked out. And I skipped over it, but I'll mention that any labeling claims for product like this would have to be tied to the pivotal trial data.

Dr. Xuefeng Li is going to give you a detailed presentation of what was a very complicated primary end point that consisted of three co-primaries and I'm not going to even attempt to do this except to give you a little preview and say that the first

primary end point looked at something called success rate. And success rate had a definition of reduction in adhesions by at least three sites or 30 percent of the number of sites with adhesions if there were more than 11. So to be a success you had to meet -- you had to have at least three fewer adhesions, I'm sorry, sites with adhesions. I beg your pardon. That is an important distinction.

And there was a -- there's a simple definition of success comparing the two groups but we felt that we would like to set the target a little bit higher and look at what lower bound on a confidence interval would really make us feel good about that success rate. So what went into that was another hurdle and that was that five percent lower bound in the confidence interval that we felt would clearly be clinically important.

The second primary end point had to do with the number of sites with adhesions and this end point, Adept patients were to be compared with themselves, only they were the control, and the third had to do with the percent of patients with fewer

dense adhesion sites at second look and this, again, compared the two groups, the Adept versus Lactate Ringers.

I don't need to read this list to you of the secondary end points, all of which we thought we agreed with the company were important, however statistical hypothesis were not predefined for secondary end points.

The basic patient demographic was, as you see, the ages early 30s. The racial demographic breakdown is as is presented in the slide, it's relatively well-balanced, possibly with the exception of slightly more Hispanic patients in the Lactate Ringers group and more Caucasian patients in the Adept, but overall they were well-balanced.

The primary diagnosis, the panel has already hooked onto the issue of primary diagnosis, how many patients had which diagnoses and the fact that you could have more than one primary diagnosis, but even taking that into consideration, the distribution is relatively well-balanced between the two groups, with respect to pelvic pain,

endometriosis, infertility and adhesions.

Baseline adhesion assessment, I don't have the standard deviation-- I only have the mean, in other words, on this slide, I'm sorry. With respect to the entire intent to treat population, a little over -- there were a little over 10 sites with adhesions and about eight and a half sites on average were lysed. There were approximately six dense adhesion sites and five out of six of those were lysed on average.

And now Xuefeng Li is going to present the bio-statistical review of the effectiveness data.

DR. LI: Good morning, ladies and gentlemen.

DR. NOLLER: We can't hear you well, please speak closer. Thank you.

DR. LI: Okay. I'm Xuefeng Li, a Statistician in the Center for Devices and Radiological Health. And I'm here to give you a brief overview of my statistical review of the effectiveness of the Adept adhesion reduction solution.

This is the outline of my presentation.

First, I will describe the statistical aspects of the study design of the pivotal trial for this PMA. Then I will relate the study hypothesis for the primary end points. I will briefly discuss the sample size and the patient accounting. And then I will present the results of the analyses of the primary and the secondary effectiveness end points. And finally, I will conclude with a summary.

The pivotal trial is a randomized double-blinded multi-center study, 227 patients were randomized to the Adept group and 227 patients were randomized to the control group. The randomization ratio was one to one. Sixteen centers participated in this study. One center had only one patient, while the other centers ranged from 13 to 75 patients. An interim analysis was conducted after 205 patients had completed the study. The overall study is deemed successful in terms of effectiveness if all co-primary hypotheses were met.

Next, I will discuss the three primary end points and their corresponding statistical hypothesis. The first primary end point is the success rate,

where the individual patient's success was defined as a decrease at the second-look laparoscopy of at least three sites if 10 or fewer sites with adhesions lysed at the first-look, or decreased at the second-look of at least 30 percent if more than 10 sites with adhesions were lysed at the first-look. The study hypothesis is that the success rate of the Adept group is larger than that of the control group by at least five percent.

In statistical terms, this end point is deemed successful if the lower limit of the confidence interval for the difference in success rates between the Adept and control groups is greater than five percent. Note that all reported confidence intervals used a level of 95.2 percent to adjust for the interim analysis conducted by the sponsor.

The second primary end point is the number of sites with adhesions. The corresponding study hypothesis is that the Adept patients have fewer sites with adhesions at the second-look compared to the first-look. Note that in this hypothesis Adept patients served as their own controls. This end point

is deemed successful if the confidence interval on the difference between the number of adhesions at the second-look from the first-look in the Adept group it had an upper limit ~~of~~ less than zero.

The third primary end point is the percentage of patients with fewer sites with dense adhesions at the second-look. The study hypothesis for this end point is that the percentage of patients with fewer sites with dense adhesions in the Adept group is greater than in the control group. Equivalently, this can be stated as the confidence interval for the difference between Adept and control groups had a lower limit greater than zero.

The sample size calculation for this superiority trial was based on the first primary end point and overall significance level of .05 and the power of 80 percent were used. The expected success rates were 40 percent for the Adept group and 25 percent for the control group. An acceptable clinical difference of five percent was specified in the protocol. The resulting sample size was 410, assuming a loss or fallout rate of 10 percent, the total

approved study sample size was 450. This is a table of the patient accounting for the pivotal trial, 777 patients were screened. Of the 449 patients who passed the screening test, 227 were randomized to the Adept and 222 were randomized to the control. This is the intent to treat population. Twenty-nine patients withdrew after treatment, 18 patients were excluded due to protocol deviations, thus, the protocol population consists of 203 Adept and 199 control patients. The two groups had very similar demographic and prognostic characteristics. The primary end points were analyzed with the intend to treat population and the secondary end points were analyzed with the protocol population.

Now, let us look at the statistical results for the primary end points. For the first primary end point the Adept group had a success rate of 45.4 percent and the control group had a success rate of 35.6 percent. The difference between groups is 9.8 percent and the confidence interval ranges from .7 percent to 18.9 percent. The confidence interval is above zero, which means that the Adept group had a

statistically higher success rate than the control group. However, the lower limit of this interval is not greater than five percent; therefore, the first primary end point did not meet the success criterion.

For the second primary end point, the number of sites with adhesions, the Adept group experienced an average decrease of 2.2 sites with adhesions. The confidence interval is below zero, therefore, the second primary end point matched the success criterion. Note that the control group by itself, also had a statistically significant reduction in the number of sites with adhesions. However, when the two groups were compared, the Adept group had a marginally larger reduction than the control group.

This table gives further detail regarding the second primary end point. We compared the number of sites with adhesions at the second-look to the first-look. These columns give the number of patients that had fewer, the same or more number of sites with adhesions at the second look compared to the first look. We can see that there are 158 patients with fewer sites with adhesions in the Adept group and 144

in the control group. In contrast, 35 and 46 patients had more sites with adhesions at the second-look. Of this 12 Adept patients and 11 control patients have at least three more sites with adhesions at the second-look. The Adept group again, appears to perform slightly better.

For the third primary end point, about 50 percent of the patients in each treatment group had a reduction in size with dense adhesions. The difference between the two groups is 1.1 percent and the P value is .73 which is not statistically significant; hence, the third primary end point did not meet the success criterion.

Before we look at the results for secondary end points, I would like to mention several statistical principles to be used when evaluating secondary end points. Generally, if the primary end point fails, it is not appropriate to use secondary end points to show the effectiveness of the device unless there has been an explicit alpha allocation plan between the primary and the secondary end points before that analysis of any data. Even if there is

very compelling evidence from the secondary endpoints to suggest that the device is effective, it would be necessary to have a pre-specified statistical plan to adjust for multiple endpoints before any statistical conclusions can be reached. Regarding the multiplicity adjustment; when there are multiple end points, the probability of claiming statistical significance for at least one of the endpoints will be inflated even if there truly is no difference between treatments for any of the end points; hence, the significance level for these comparisons must be adjusted downward in order to control the overall error rate of five percent.

Even though the study failed, the overall success criterion for the primary endpoints, let's look at this table which gives some of the secondary endpoints and corresponding P values provided in the PMA. All comparisons with P value less than .05 were included in this table. Note that in the table summarizing the secondary endpoints in their PMA the sponsor presented a total of 24 comparisons between the two groups.

In summary, the results are consistent with the analysis of the primary end points. The Adept group showed an improvement over the control in most of the secondary end points, though some of those P values were less than .05. We must also note that none of this analysis took onto account the multiplicity of end points. In order to adjust for these multiple end points, a multiplicity adjustment needs to be performed. Generally, the greater the number of end points, the greater the adjustment needs to be, and the greater the adjustment, the smaller the P value would have to be in order to be considered significant.

Since the sponsor has presented some results as well as P values for secondary end points, I have explored several of the possible multiplicity adjustments to evaluate the degree of evidence that could be drawn from these secondary end points. Although the sponsor had a pre-specified multiplicity adjustment plan, there are various ways to do this. The methods that are considered here were the modified Bonferroni correction and Holm's step-down method. I

will not talk about the details of these methods here. You can find the more detailed discussion of this in the Executive Summary. After adjustment, it appears that only the endpoint percentage of patients with reduction in AFS goal might be significant. The unadjusted P value is .001.

Now, for a brief summary of the effectiveness analysis for the Adept solution. The study met only one of the three co-primary end points. For the first primary endpoint, the difference between the success rates was not shown to be greater than five percent. For the second primary end point, there was a significant decrease in the number of sites with adhesions over baseline in the Adept group. Finally, for the third primary end point, there was no significant difference in the percentage of patients with fewer sites with dense adhesions at second-look.

Regarding the analysis of the secondary end points, no firm evidence of effectiveness can be drawn with adequate statistical validity. Okay, this is the end of my presentation. Now, I will turn the

podium to Dr. Carey-Corrado again. Thank you very much.

DR. CAREY-CORRADO: What I wanted to do was just present adverse event data possibly from a slightly different perspective. The reason is that the panel pack gave you a whole lot of data on safety, presented a lot of different ways and it's hard to distill it. We thought it was useful to look at adverse events that occurred within seven days of the first laparoscopy and thank you very much, and the more of those events that were reported within the first seven days, the relatively most common ones.

So as you can see here, headache, abdominal pain, dysurea, vaginal bleeding, vulvar edema, vomiting, diarrhea and fever occurred at relatively higher rates than other reported adverse events. The only thing I will take your time here to point out again is the rate of vulvar edema in the two groups and interestingly, possibly just coincidently, but in the first pilot study the rate of vulvar edema was six percent. There were two cases, I think, in around 35. In the second study, in RAPIDS, it

occurred on one in 25, that was a rate of around four percent, so we might be seeing here what would be the expected rate of that adverse event following use of Adept. But we don't see any remarkable trends in the rest of these data.

Pain is something that we consider an important review issue at FDA when we're looking at adhesion barriers, reports of post-op pain, and so we looked at it. And looking at it from this standpoint, this was not restricted to the first seven days, so this was any time during the conduct of the trial, and you can see that the rates of post-operative pain, pelvic pain and abdominal pain, are more or less similar across the two arms of the study.

But we will -- while the review is in process, we'll continue to scrutinize the data. With respect to serious adverse events, there were four serious adverse events, that is events that got the classification serious that FDA concluded from its review thus far. One of the Adept related adverse events the investigator did not attribute to Adept and if I am not mistaken, that was a serious adverse event

that involved readmission of a patient whose presentation included labial swelling. And we felt that it was reasonable to conclude that that part of her readmission was related to the device. So there were in conclusion, two Adept-related serious adverse events, two Lactated Ringers patients who were also readmitted for the events that you see listed here.

That really is an overview of our safety review to date and we've tried to highlight what we think is the most significant adverse event that is related to the product that is the labial or vulvar edema. At this time, I'm going to try to preview the discussion questions for this afternoon and as a prelude to that, just remind everyone that the proposed indication is as an adjunct to good surgical technique for reduction of post-surgical adhesions in patients undergoing gynecological laparoscopic surgery which may include adhesiolysis. There are a number of components to that proposed indication for use that we'd kind of like you to keep in the back of your mind during your deliberations.

Discussion question one, first, in the

first paragraph it summarizes the fact that there were three co-primary endpoints and it summarizes the outcomes for each of those analyses. Our concluding question for the panel deliberation is, although the statistical hypothesis for only one co-primary was met, please discuss each of the primary endpoints considering the objective, the statistical test and the clinical significance of those end points.

Regarding co-primary end point one, there was a greater reduction in the sites with adhesions for the Adept group. That didn't reach -- the lower bound of the confidence interval was above what we had set as the target. Lactated Ringers performed better than expected. The study was powered for Lactated Ringers' performance at a rate of around 25 percent and the success rate was actually 35 percent.

The second co-primary looked at the difference in the number of sites between the second and the first look, and you can see the results here. We even have data here comparing the two groups, but I want to point out an important difference in this slide compared to how you've seen that second co-

primary presented earlier. The first time around we looked at the co-primary for everybody and as you all know, a bunch of those patients in the intent to treat population were successes, so it didn't seem to make sense to look at who got worse at second-look when you included a whole bunch of patients who actually had improved. So what we did here was we subtracted out the patients who were successes from the intent to treat analysis and then we asked the question, did women get worse. If they weren't a success, did they get worse and how much worse did they get?

And you can see here that if they did not meet the definition of success, they really didn't get worse between first and second look or by a negligible amount.

The third co-primary end point was to look at the decrease in dense adhesions and what we had wanted to test was whether the Adept patients had fewer dense adhesions at second look compared to Lactated Ringers. And as you've heard, there was no difference in the two groups. However, in both groups the patients improved by a mean of one. That is, they

had an average of one fewer dense adhesion at second look.

Discussion question two has to do with the secondary effectiveness end points. You have in the handout on the panel discussion questions a long list of those endpoints and what we would like you to pay close attention to and I'm sure you obviously are going to be talking about the infertility patients and the AFS scores for that patient population. We'd like you to discuss the clinical significance of those outcomes.

As Dr. Li has said, when the primary hypotheses aren't met, we have to look at secondary endpoints cautiously. However, even after the multiplicity adjustment, there is an improvement in AFS score for infertility patients. This is just a review of the AFS scoring system. I don't need to, for this audience, go through that first bullet but I would like to make a couple of points. The mean baseline score, AFS score, in the infertility patients in both arms was between eight to nine points and again, that's just the infertility patients, so you've

seen a slightly different number for the overall patient population. In the two populations there was a mean improvement by minus three points for the Adept patients and minus one point for the Lactated Ringers patients. Again, those are means but that's in general, the magnitude of the improvement when you look at it from the standpoint of that scoring system.

This is another way to look at that and I'm going to summarize this by saying, as you look at this table, 31 patients in the Adept group and 56 in the Lactated Ringers group really didn't change. There was no change in the AFS score. However, when you look at the scores, the patients who improved by anywhere from five to around 20 points, 30 Adept patients had improvements between five and greater than or equal to 20 whereas, only 20 -- well, 20 of the Lactated Ringers patients showed a similar magnitude of improvement and in that discussion, I didn't mention the patients who improved by a score of minus one to minus four.

In terms of getting worse, increasing your AFS score from five to greater than or equal to 10,

there were six Adept and 10 in the Lactated Ringers group. So what we're trying to achieve is just give you greater depth in your feel for what the difference in AFS scores between the two groups were and what the magnitude of the difference was.

I also want to mention pregnancy outcomes and I want to make it clear that the sponsor has never used the pregnancy outcome data in support of the PMA. We think it's interesting to note that 81 Adept and 91 Lactated Ringers patients were followed for 12 months for fertility and there were 14 live births among Adept, 21 in the Lactated Ringers group. We know that at least 19 of those patients underwent some sort of assisted reproductive technology. Unfortunately those data were not collected at this site. So although the panel in 2001 indicated an interest in this kind of outcome, they said you could look at it post-market, we nevertheless thought it was kind of interesting to present that today, although, again, we can't draw any conclusions because we don't know who had IVF.

Discussion question 3 has to do with the

safety data. We'd like you to discuss any adverse events including vulvar edema that you believe are related to Adept and whether you believe that any risk posed by Adept is outweighed by the clinical benefit as you will have discussed under Questions 1 and 2 above.

Dr. Baoguang Wang is going to be talking about the ARIEL post-market registry that included both gyn and general surgery patients and this is an unusual situation that we have a lot of post-market data for this product from European experience and we'd like you to discuss whether the safety data from the ARIEL registry supports the safe -- the conclusion that Adept is safe as an adhesion prevention solution. With respect to labeling, we'd like to invite any comments the panel may have on the proposed labeling. We would, in particular like the panel to talk about the proposed indication for use as the company has presented it and whether and to what extent the clinical trial data support the indication for use or a modified or narrower indication.

And Dr. Baoguang Wang also will be

presenting kind of the guidelines surrounding post-market studies and what FDA can ask for as -- in terms of asking a sponsor to conduct a post-market study, whether the panel would have any input after hearing Dr. Wang's presentation regarding any issues that should be addressed in a post-approval study.

So in summary, this was from our review. It appears to us this is the first investigator blinded RCT. The sponsor will be addressing the issue of study blinding. The primary endpoints were challenging. LRS performed better than anticipated and we have not seen to date any serious Adept related safety issues at this state or at this stage of our review. At this time, I want to introduce Dr. Baoguang Wang. Thank you.

DR. WANG: Thank you. Good afternoon, everyone. I'm Baoguang Wang and I'm Epidemiologist on the FDA review team for this PMA. So far you have heard presentations about performance of Adept, about 450 patients in the pivotal clinical trials. And now I'm here to present information more than -- on the performance of Adept in more than 4,000 patients

outside of the US. I will also discuss something -- some principles of post-market expectations.

During my presentation, I'll give you a brief review of the registry, in 4,620 patients and I will also discuss general principles of post-approval studies. Now, I'd like to give you a brief review of Adept Registry. Adept Registry for Clinical Evaluation or ARIEL was established in the United Kingdom in 2000. The objective of the Registry was to gather and share surgeons' experience in the use of Adept and to monitor adverse events in patients treated with Adept.

The Registry was voluntary and consisted of a gynecology registry and a general surgery registry. A total of 253 centers in six European countries participated in the Registry. The participating centers were selected on the basis of their beginning use of Adept as a part of a routine surgery. In the beginning of the Registry, surgeons from leading centers were asked to report their first 20 to 30 patients treated with Adept. Over time, the participation was broadened to include small centers.

However, the sponsor did not provide the information of how many patients treated at large centers or small centers.

Now, let's look at the population in the Registry. Between February 2000 and December 2003, the ARIEL Registry captured that data on 4,620 patients representing eight percent of the 56,000 patients treated with Adept at the time of the closure of this Registry. Of the 4,620 patients in the Registry, less than half of the patients underwent laparoscopic surgery for gynecology procedure, which is the procedure the device is intended for use in the US.

Data collection were done with a five-page physician data collection form. The information collected on this form included the patient's demographics, medical history, surgical procedures, use of Adept and surgeon's experience with handling Adept and their clinical observations and also complications and adverse events during and after surgery. Adverse events were also -- data were also collected post-discharge, but the post-discharge

adverse events were collected on the basis of spontaneous patient self-report.

And one thing I'd like to point out here is patients' demographics information included patient's age, height and weight. No race, ethnicity information was collected or no other demographic information was collected for the Registry. One of the many functions of the post-market Registry is to collect the data on adverse events, especially rare adverse events that are not usually observed in clinical trials. ARIEL Registry collected the information on adverse events. Overall, there were 755 adverse events reported to the Registry representing about 16 percent adverse event rate.

The adverse event rate is the lowest in the gynecology laparoscopic patients, followed by gynecology laparotomy patients and general surgery laparoscopic patients. The highest adverse event rate was observed in general surgery laparotomy patients. This table shows five most frequently reported adverse events in the gynecology laparoscopic patients. Out of 2,069 patients, there were 12 cases of abdominal

pain representing adverse event rate of .6 percent. As you can see here, all the adverse event rates are less than one percent. Please keep in mind that these data are from the voluntary registry which has major limitations, such as on the underreporting of adverse events, and lack of detail information for ascertainment of adverse events.

This table shows the five most frequently reported adverse events in about 1500 general surgery laparotomy patients. I understand that the Adept is not indicated for use in general surgery laparotomy patients. I'd like to present the adverse events data here to call your attention to the potential problems with off-label use of this device. As you can see here, not only the adverse events rates in these patients are higher but also more serious. In addition to the adverse events listed here, there were 10 cases of death and six cases of peritonitis reported to the general surgery registry.

An assessment of the ARIEL Registry, the objective was clearly defined but it was a broad and non-specific. The participation of the Registry was

voluntary and targeted to surgeons from leading centers initially. There is no information on what percentage of the patients treated at the leading centers or small center and no information on what constitutes a leading center or a small center. While a total of 4,620 patients were included in the Registry, the Registry data represents about eight percent of all the patients treated with Adept at the time of the closure of the Registry and less than 50 percent of the patients underwent the procedure that is indicated for use in the US.

The Registry data covered multiple domains but there was no information on race ethnicity and post-discharge adverse events data were collected based on patient self-report. Sorry, I go too fast. Although the Ariel Registry data showed that adverse event rate was relatively low in general in the gynecology laparoscopic patients, it was much higher and more serious in general surgery laparotomy patients. While the Registry data seems to have provided additional reassurance of the safety, the use of Adept in gynecology laparoscopic patients, this

Registry data should be evaluated in the context of the quality of the voluntary registry data.

As I just mentioned, this registry data represents eight percent of the patients treated with Adept at the time of the closure of the Registry. Less than 50 percent of them underwent the procedure that's indicated for use and post-chart adverse events were data were collected on patients self-report basis which is likely to be under-reported because the data collection on adverse events with the voluntary registry is usually much less rigorous compared to closely monitored clinical studies. Finally, the ARIEL Registry data suggested that there might be a potential problem with the off-label use in the US.

Now, I would like to talk about the post-approval studies. This afternoon there will be a discussion about a potential need for a post-approval study for this device, which is indicated in Panel Question Number 4 and 6 in your panel pack. To help the panel members to understand the post-approval studies and what is some general principles of post-approval studies, what we can and cannot do in the

post-approval studies and I will also talk about under what circumstances that we need post-approval studies.

The objective of conducting post-approval studies is to evaluate a device performance and the potential device related problems in broader patient population over an extended period of time after pre-market determination of reasonable device safety and the effectiveness. Post-approval studies should not be used to evaluate unresolved issues from pre-market phase that are important to initial determination of device safety and the effectiveness.

The reasons for conducting post-approval studies are to collect the post-market information including longer term performance of the device, community performance which is the device performance in a broader patient population treated by average physicians as opposed to highly selective patients treated by more experienced physicians in clinical trials. Post-approval studies are also needed to evaluate the effectiveness of a training program for use of the device and to evaluate the device performance in a sub-group of patient population since

the clinical trials tend to have limited number of patients which may not include all sub-groups of the general patient population.

In addition, post-approval studies are also needed to monitor adverse events, especially rare adverse events that are not usually observed in the clinical trials. Another reason for post-approval studies is to address issues and concerns that panel members may raise based on experiences and observations panel members may have.

To summarize my thoughts regarding the ARIEL Registry, the Registry data seems to have provided additional reassurance of safety in the use of Adept in gynecology laparoscopic patients. Based on the Registry data, it appears that Adept does not cause -- does not cause long-term negative impact on gynecology laparoscopic patients. While the Registry collected the information post-market experience on the use of Adept outside of the US, it only represents 8 percent of the patient population at the time of the Registry was finished and less than 50 percent of the patients underwent the procedure that's indicated for

use in the US.

In addition, the long-term safety data were collected based on the patient's self-report which is subjected to under-report and incomplete information. Adept is intended to be used in routine gynecology laparoscopic surgery and no training for use of Adept is indicated. The Registry captured the data on a relatively broad patient population outside of the US compared to the patients in the clinical trials.

And finally, the ARIEL Registry, especially gynecological registry data does not seem to show serious adverse events related to Adept as the time -- as the status the review team is at. Based on what I have presented, the Registry data should be interpreted with some caution given the voluntary nature of the Registry data and the other noted limitations. With that, I conclude my presentation, thank you very much.

DR. NOLLER: Thank you. You'll notice on the agenda that we have 20 minutes set aside for questions and answers. We're running behind by about

that amount of time, but I don't want to skimp on the time we have to ask questions of the sponsor and the FDA, having heard their presentations. Some of the questions, hopefully, will be straightforward and the sponsor or FDA can come to the microphone and answer them quickly. Others may take some research and we will give them some time later to answer those questions after lunch.

Having heard both presentations, does the panel have additional questions at this time? Yes, Howard.

DR. SHARP: I had a question. Do we know whether the --

DR. NOLLER: I'm sorry, please address it to either the sponsor or the FDA at this point.

DR. SHARP: This could be -- I guess I'll ask the sponsor. Do we know whether the patients with labial edema were the same patients that had inability to void?

DR. NOLLER: Do you wish to answer or do you want to wait?

MS. CLISBY: Could we take that question

after lunch, because we do have some slides to show you about labial edema? Could we address that at that time?

DR. NOLLER: Fine, thank you. Yes, Dr. Cedars.

DR. CEDARS: This is for the sponsor. One more question about the blinding and the product and while it's clear and odorless like the Ringers, and it's considered non-viscous, was there any difference because your primary end point was judged by the surgeon themselves and not blinded by the video review, was there any difference either in the viscosity intra-abdominally or in the interaction between the substance and blood as you were doing a dissection?

DR. NOLLER: Do you wish to answer now?

MS. CLISBY: I'd like to ask Dr. Luciano to answer that question.

DR. LUCIANO: Good afternoon. My name is Anthony Luciano and I'm Professor of Obstetrics and Gynecology at the University of Connecticut and I was one of the principal investigators and we enrolled

several patients, I don't remember the number, but exceeded 50 and we really could not tell the difference. There was no difference in color. There was no difference in how it mixed with the peritoneal fluid or with the blood. You really could not tell. There was no difference in viscosity either.

DR. NOLLER: Thank you.

MS. CLISBY: Perhaps Dr. Martin, since he was --

DR. MARTIN: Dr. Dan Martin, Clinical Professor, University of Tennessee at Memphis. I have no additions to that.

DR. NOLLER: Dr. Miller, you have a question?

DR. MILLER: Yeah, I have questions for both. To the FDA, a lot has been made of the five percent lower boundary for the confidence interval and I guess I'd like some more discussion about why that specific boundary was chosen, what was the rationale and since we're holding the sponsor to that standard, I think we need to understand the importance of that rationale in our deliberations? For the sponsor, my

question is, for that cohort that seemed to do worse in terms of adhesion formation, does the sponsor have any speculation about which patients may do worse? In other words, was there any profiling done or any further subsequent analysis done to better understand why some patients just do form more adhesions with respect to Adept?

And I guess the last question I have is maybe for both, which has to do with can we interpret any of the experience from the other product, I think it's Extraneal, relative to the safety for this product? In other words, given that they're both placed in the peritoneal cavity, although at different concentrations, can we -- since there's been so much experience with the Extraneal product, can we infer that they're likely to be comparable in terms of safety profiles?

DR. NOLLER: FDA, do you wish to address either one of those at this point?

DR. CAREY-CORRADO: My name is Julia Corrado and I'm going to first address the issue of the five percent. Historically, we had, in looking at

adhesion barriers, found ourselves in positions where we only -- we had a limited amount of effectiveness data and it was real marginal. So to be quite honest, we thought that this time around, we wanted to set a real high boundary so that we could have a better or more comfortable feeling that there was some clinical benefit and we thought that based on the pilot studies and what we knew about Adept, that it was -- this was going to be an achievable goal. So we were trying to be fair to the sponsor but we were also trying to be fair to ourselves in that we wanted to entertain the review with -- I guess, with a -- with a level of evidence that was better than the minimal threshold that we might be presented with. So I don't know if that helps but that's an effort to answer the question.

DR. NOLLER: Thank you. Does the sponsor wish to discuss the second or third questions that were addressed to them?

MS. CLISBY: I think I'd like to invite Professor Piantadosi to discuss the confidence interval issue that was raised.

DR. NOLLER: Dr. Miller, you didn't address that to the sponsor. Would you like to hear their comments?

DR. MILLER: Certainly.

DR. PIANTADOSI: Thank you, Dr. Miller. MY name is Steven Piantadosi. I'm a Professor of Oncology, Vital Statistics and Epidemiology at Johns Hopkins. I, obviously, wasn't part of the FDA response or deliberations with regard to the five percent rule. However, had I been present, I would have argued very strongly against it for the following reasons. To have a 95 percent confidence interval live above a five percent tolerance, that's equivalent to having the 99.9 percent confidence interval live above zero. So the operational consequences of this five percent rule have been to restrict the Type 1 error for the primary comparison to 0.1 percent rather than to the usual 2.5 percent that we would expect from a two-sided five-percent rule.

It's interesting to note that in the FDA's own presentation they set the alpha level at five percent, indicating that they were willing to accept a

two and a half percent chance of making a directional Type 1 mistake in the presence of the five-percent boundary.

The reason the five-percent boundary is not very good is evident now, because we have what could be viewed as an ordinary masked randomized trial with a fairly strong standard of evidence in support of the study drug being superior to what is ostensibly a placebo, although a placebo with a slight volume effect, and yet, we're having difficulty evaluating the evidence because we put on ourselves this strict rule of 0.1 percent Type 1 error.

We don't do that for any other kinds of studies. In fact, for most clinical statistical and regulatory purposes, we have no need for such a stringent Type 1 error as implied by the five-percent rule and that's why I think the panel has to deliberate around it and look at the consequences of that five-percent rule in terms of the Type 1 error.

DR. NOLLER: Thank you. Sponsor, you were asked if you had done profiling to determine perhaps who would do worse. Do you wish to address that

question at this point?

MS. CLISBY: Yes, Professor diZerega will answer the question.

DR. DiZEREGA: Thank you for your question. This has been a question that a lot of us have been quite interested in throughout all the adhesion prevention studies since the first laparoscopic study back in 1979 and 1980. In this particular situation, looking at the patients that did worse, we have tried to find any correlative value that would have predicted even post-hoc even retrospectively that patient population to identify them with any kind of exploratory analysis and this large population of patients, we thought we had a reasonable chance of finding something that made clinical sense and the answer is, we have not.

There is not anatomical juxt position of adhesions. There's no medical condition, there's no predisposition of anything that we've been able to even identify to the point of generating a hypothesis. Having said that, I do think it's a clinical experience that we've all shared during the same type

of operation on two different women who have fundamentally the same pre-existing condition and finding that in a small population that group of women do very poorly from the standpoint of adhesion formation such that there are the concept clinically of adhesion formers.

Our group in Los Angeles and others have tried to identify pre-disposing factors and in fact, there are pre-disposing factors relating to alternations in plasma and activator activity that predispose a small population of patients to even forming more adhesions than the population on general. We all form adhesions, but it looks like some of us are at special risk.

Having pointed that out, we have not gone back to the population you asked about and done these kinds of analyses on these patients, but I think this is an important opportunity that we don't want to pass up.

DR. NOLLER: Thank you. I just received some terribly important information. The restaurant closes at 2:00 o'clock. So let's do this. Let's get

more questions from the panel because some of them might be something you'd want to work on over the lunch time and then we will break in about five minutes for lunch. Dr. Snyder, you had a question?

Dr. SNYDER: I actually have two questions, both directed towards the industry. My first is, since you know, any approval of the indications would include its use as an irrigant, was there any attempt at any sort of data collection, you know, to justify a recommendation for use as an irrigant, I didn't see that, you know, versus any other irrigant?

And then my second question is, is throughout these studies, it seems to be a large amount of individual variation between how long the solution stays in the peritoneal cavity. And in other words, in some of this -- was there ever any attempt to try to quantify, you know, the length of time you know, that -- you know, in other words, measure volumes of solution, you know, from the point of post-op, you know, through days 1, 2, 3, because it seems like if there is a large amount of variability in how

long the solution is going to stay around then that's going to significantly effect, you know, outcome.

DR. NOLLER: Go 1, 2 3 for the questions here. Yes.

DR. SHARTS-HOPKO: I'm interested in knowing, in addition to the labeling, what training strategies have been used in European marketing?

DR. NOLLER: Dr. Weeks?

DR. WEEKS: I've got two questions. I may have missed it in the protocol but were uterine manipulators used in the surgeries and for the FDA, we saw several exploratory covariant analyses in which the P value for centers effect seemed to be statistically associated with a much stronger probability of desired outcome than the treatment effect. And yet the treatment by center interaction was insignificant and how much of this is due to just small sample size.

DR. NOLLER: Thank you. Dr. Chegini?

DR. CHEGINI: I keep making this -- this question is either to Dr. Li, who did the statistical analysis and also to industry. My question in regard

to two group of population, the one that they have only adhesion versus the one they have adhesion and endometriosis because we are dealing with a totally different population. The one with endometriosis tend to have much more inflammatory environment in the peritoneal cavity than the one with the adhesions, so if there is any differences in there.

The second question is, in the term of glucose concentration, it is very well established that the glucose content can have an adverse effect on ovulation and the -- so if your patients are going to infertility clinics and so on, what kind of effect there is because as you show, the live birth between your treated group versus the one that they did not receive anything was substantially different.

DR. NOLLER: Dr. Isaacson?

DR. ISAACSON: Yeah, a quick question to the sponsor; one, how did you derive the scoring sheet that you have that seems very complicated? Has it been used in other studies validated? Where did it come from? And two, because it is so complicated and detailed, when -- at what point during the surgeries

or after the surgeries were the surgeons required to fill this out? Was it within an hour, was it after looking at video or what have you?

DR. NOLLER: Dr. Sharp?

DR. SHARP: In regards to labeling, are you going to -- will this be limited to clean cases as was performed in the pivotal trial and also in Europe is it restricted to clean cases? I noticed in the ARIEL data that there were a number of an estimative (phonetic) patients that had clearly clean contaminated and I just wondered if the 28 percent adverse event rate was correlated at all to those perhaps clean contaminated cases.

DR. NOLLER: We have exhausted our 20 minutes. Before we take a lunch break, let me remind the panel not to speak among yourselves about the matter at hand and also not to talk to the sponsor or competition. For the panel, there is an area set aside in the restaurant to the left, I understand, as we go in. It is 1:14. We'll re-adjourn at 2:14.

(Whereupon at 1:14 p.m. a luncheon recess was taken.)

DR. NOLLER: I would like to call the panel back to order, please. Has everyone turned off their cell phones? Have order, please. Discussion please stop in the audience. Thank you.

Now there may be a few more questions from the panel, but before we get a thousand questions and no answers, let's go with the ones we have, and then we'll see if there are other additional questions. And we'd like to ask the sponsor to go first. And each person, everyone who's already been up doesn't need introduction again.

Also, I'd like to instruct both the panel and FDA to please try to answer the questions directly and not bring in extraneous stuff for new studies. In other words, be efficient, and please hold the answers to a minute or two, because I think most of the questions are fairly straightforward. So, sponsor, you want to begin.

MS. CLISBY: Okay. Thank you, Mr. Chairman. The first question was in relation to the ARIEL registry. My other question, I wanted a little more data, so we put together a backup collection of a

few slides that speak to that. So it was established to allow surgeons to record and report their experiences of the use of Adept in routine surgery, and it was conducted between September 2000 and December 2003. So the surgeons were invited to record the outcomes of all their operations using Adept. And the last bullet point speaks to the gynecological surgery. The next slide.

DR. NOLLER: So it was voluntary.

MS. CLISBY: It was voluntary, yes. So this slide shows you the data which was collected. There was specific data collection forms for gynecology and general surgery, and this shows you the sort of data that was collected. I want to just point out that in relation to the Ampercy Benett data collection, all of this data was collected while the patients were in hospital, and although the surgeons were asked to record their view about the relationship to Adept, all of the data which you've seen just reports the events, and so it doesn't mean that they were or were not related to Adept. They may just have been related to surgery or not. And the next slide.

This shows you -- I won't read the slide, but for you to read -- the demographics and surgery performed in the gynecological registry. And the next slide. This gives you the presenting conditions and symptoms in the gynecological surgery registry. So I hope that answers that ARIEL question.

The second question was related to the video audit procedure, and I'd just like to invite my colleague, Elizabeth Peers, to answer that question.

DR. PEERS: Thank you. I think the question here was about any effect that the process of the video review or the video reviewer had on the outcomes in the study. Just one or two other comments; the study was, of course, double-blind, and we know that the FDA was satisfied that on video there was, indeed, no difference to be observed between the adax and the Lactated Ringers solution, so we know that the blinding was very convincing there.

We had, also, no -- the protocol requirements was that the first look video, in other words, the one at the time of the initial procedure, had to be reviewed before that for the second look, so

in that sense, there was no blinding because there was a need to look at the first look video before the second look. Next slide, please.

Right. To move back to the question about whether the process of the video review actually had any effect. About half the patients in the study -- all were videoed, but about half the patients had no reviews of their videos, so here we're looking at a comparison of the half in red -- I beg your pardon -- of those who had no video, and those who did. Now on the left side of this slide, here we have all patients, all the patients and the outcome in terms of AIRFES scores, and also for the infertility patients separately, with and without audit. So here we have the percentage of patients, and here we have Adept group here and the Ringer's group on the right. Here we have those who have no audit. You see exactly the same results.

DR. NOLLER: Excuse me. What does the word "audit" mean?

DR. PEERS: It means that they were reviewed by the video reviewer.

DR. NOLLER: Thank you.

DR. PEERS: Those who have no audit, no review, and these who did; again, exactly the same results. There were some who had no queries, most of them, the majority; again, same results. And, indeed, some that did have queries; again, the same result. Next slide, please. Just to show that's not cherry-picked, I've got two or three more.

Here's look at the dense adhesions, again, an analysis of those with and without audit, it's exactly the same, the entire patient population, those who did not have an audit and those who did have an audit, those with no queries and those with queries, essentially similar results, while in this case the Lactated Ringers group appears better.

DR. NOLLER: Follow-up on that?

DR. EMERSON: I just want to make sure that when you're showing me the audit, are those the results from the audit? And when you're showing me the no audit, obviously, those are the results from the investigator?

DR. PEERS: That is correct. Would you

like to comment, Alison?

DR. SCRIMGEOUR: Alison Scrimgeour, biostatistician. These scores, once the audit had been conducted, the investigator, if he agreed with the score and it was reported in the CRF, and that CRF is the analyzed score, so we have the final agreed score, and that's what's been analyzed in each case, so these are the analyses of the patients, those that did have an audit, those that didn't have an audit. And if there was an audit, those that had queries and those that didn't have queries.

DR. EMERSON: And the queries were those where the investigator and the auditor did not necessarily agree.

DR. SCRIMGEOUR: Yes, but the final score was that, that the investigator agreed with, so they may or may not have had a change as a result of the queries.

DR. PEERS: Thank you. Next slide, please, just again, further again, looking at success. This is the primary efficacy outcome, so success as we previously heard described, and again, exactly the

same presentation. The results for the entire group which you've seen, 45 percent versus 35; again, the same result for those who've had no audit, and very similar again for those with. And again, with queries here -- sorry, no queries these two bars -- and then with queries, so essentially similar results whatever the process. Next slide.

Just to show you a slightly different variation -- not a very interesting set of slides -- this is looking at the reduction in incidence, and that's why the slide is displayed in this way. So here is zero, no change in incidence, and then the reduction in incidence, which, of course, you will remember is related to the second primary end-point. Again, Adept is on the red bars and Ringers Lactate on the right. And this one is just slightly different from the others. Apart from being upside down, here is the entire group, those with no audit, and those with audit, those with no queries, and those with queries. Now here, where there's queries, which means there's a discussion between the video reviewer and the investigator; in fact, it appears as though the

LRS patients did better. However, of course, this does not affect the overall results, so that just shows you that the process itself did not, in fact, benefit Adept at all to any extent.

DR. NOLLER: Okay. Thank you.

DR. PEERS: Thank you.

DR. NOLLER: Michelle, did you have a follow-up?

DR. CEDARS: Yes. I'm not sure that this presentation really addresses the issue of the video report, and this is what you're getting at; because if you had this designed such that you looked at the scores from the video report compared to the scores from the investigators and compared them in a blinded fashion, but to just say these subjects were audited and these were not, to me, isn't the same as answering the question of the validity of the surgeon's report. So I'm assuming that you don't have that data, especially since you said the first videos were always read at the first, so there's no way that the video reviewer was ever blinded as to which was first and which was second.

DR. PEERS: That is correct that there was no blinding with respect to which video was first. The reviewer always knew which was first. But in any case, certainly by the process of the use of the device, that would have, in any case, been evident.

DR. NOLLER: Dr. Emerson.

DR. EMERSON: Can you just comment on, in particular, the second of your three endpoints with regard to this blinding? So your second of your endpoints, which is basically a single-arm end-point, where you're just looking to see whether there's been a decrease in adhesions, and whether this auditing process protected us at all from bias in that end-point.

DR. PEERS: Well, I would emphasize again that this is a double-blind study, as confirmed by FDA.

DR. EMERSON: But since that's just a one-arm comparison, any bias that comes from everybody expecting there to be fewer adhesions later, that they just knew that, they knew that going in. Right?

DR. PEERS: Well, if that were the case,

it would be biased in the same manner for both groups. Does that answer your question?

DR. EMERSON: Except for the secondary end-point, as I understand it. I mean, I'm sorry, the second of the three co-primaries as stated in the protocol, though, was not the comparison between the two arms. It was just the single Adept arm comparison.

DR. PEERS: That is strictly correct. Yes. Could Dr. Martin have a comment here, as well?

DR. NOLLER: Yes.

DR. DAVIES: For some of us who've done a lot of adhesion studies, our anticipation would have been opposite what you said. My anticipation is that my second looks frequently look worse than my first, so I'm not sure what anticipation had to do with that second look. Some of us anticipated getting things worse.

DR. NOLLER: Next question, please.

MS. CLISBY: I think the next question related to how well matched the groups were for the analysis of the secondary endpoints, and I'd like to

ask Dr. Peers to answer.

DR. PEERS: Yes. Thank you again for the opportunity to clarify this issue. Here we have, in the same manner as I presented earlier on for the baseline adhesion assessments for the entire patient population, here we have the pelvic patients -- that is to say, those patients who had a diagnosis of pelvic pain, primary diagnosis of pelvic pain when they entered the study. And here, you can see the Adept patients - 152, LRS - 134, and exactly the same parameters listed down here on the left with the incidence of adhesions 10 in each group, 8.5 approximately of which were lysed, very similar extent, very similar severity. Again, six dense adhesions of which five or so were lysed. The AFS score in this group is actually a little lower, but I don't think that's meaningful given the standard deviation we see here, 6.4 plus or minus 8.8, and 6.1 plus or minus 9.4. And again, a similar number of sites with endometriosis.

Remembering that this is actually quite a large subgroup, around 60-65 percent of the patient

population, it is not surprising that they match pretty well with, of course, the entire group.

Moving on to a different set of patients, this is those with a primary diagnosis of infertility. And here we can see again, the Adept and the Ringers groups, how well matched they are. And I don't think I want to take up the panel's time with describing every one, but suffice it to say that these are, again, reflecting well-balanced numbers across the two groups, reflecting the success of the randomization procedure.

DR. NOLLER: Perhaps, can I ask you, did you look -- if you looked at these for all of the various subcategories, were they all approximately the same?

DR. PEERS: I think the short answer to that is yes, but I'd like to invite my colleague, Ms. Scrimgeour, to comment.

DR. SCRIMGEOUR: I've just looked at lunch time, and the categories I've looked at, they're all the same, broadly speaking.

DR. NOLLER: Thank you.

DR. PEERS: Thank you. Is that sufficient?

DR. NOLLER: Marcelle.

DR. CEDARS: Can you go back to the prior slide just a minute?

DR. PEERS: Yes.

DR. CEDARS: So was this also intention to treat, or was this the ones that were analyzed and had the second laparoscopy, and why did you use specifically intention to treat in the infertility group, or was that different, because that was really the group where you saw significance in the secondary analyses. So if you looked at the patients that you -- so go to the next slide now. Then you say that that's your intention to treat group, and yet, because your scores were based on the second look, did your data of the ones who actually came back for the second look, look the same? I mean, why is there a difference between those two slides?

DR. SCRIMGEOUR: We had the infertility patients readily available, the pelvic pain I had to work out. It was quicker to do per protocol, which is

probably not a good answer, but that's the long and short of it. There were only 29 patients that didn't come back for a second look. I don't think it would have made a great deal of difference to how this looks.

DR. NOLLER: Actually, we were told all the secondaries were per protocol.

DR. SCRIMGEOUR: They were. They were.

DR. PEERS: Yes. And just a point of clarification, and actually baseline -- of course, this is the entire group because this is at baseline, says nothing about second look. This is the baseline adhesion assessments.

DR. NOLLER: Right. So they're all in the intention --

DR. PEERS: So they are all intention to treat, if you like, but it's at the point of entry to the study.

DR. NOLLER: All right. Next question, please.

MS. CLISBY: I think the next question related to overlapping diagnoses, where patients have

more than one. And I'll as Professor diZegera to speak to that one.

DR. diZEGERA: What we've done is tried to address the answer to that question in two ways; one, to show the distribution of the patients, and then to show how, very briefly, how the results turned out when a patient had multiple diagnoses. So first, let's look at the distribution. The Adept patients in this analysis are shown for you on the left-hand portion, the LRS patients on the right-hand portion. This is the distribution with single entering indication infertility, endometriosis, pelvic pain. And then as you combine them, you can see how the numbers look, and for this kind of a study it's pretty well balanced across these different categories. Next slide, please.

If you look then at the results of these patients that have multiple indications, let's take first the patients with endometriosis and infertility, and these are, of course, Dr. Noller, the ones that had second look laparoscopy. I want to point out, this is an exploratory observation. This is not

something that was in the protocol. This is a specific slide to answer a question from the panel, and we're talking about the percent of patients now that had a reduction in the adnexal adhesion score with multiple diagnoses. You can see the number of Adept patients, the number of Ringers lactate patients, very similar. The difference in terms of the percentage of patients with a reduction in AFS score is about 30 percent.

I'd make an editorial comment that in general what we see with this data set, as the more complex the adhesion-related diseases are, the more separation we can see between treat and control. Is there another slide, Alison? Yes. The other one is endometriosis and pelvic pain, combined as I said a moment ago, and you can see the number of the Adept patients, number of LRS patients. And once again, there was a relative difference in favor of Adept with these multiple diagnoses. Thank you.

MS. CLISBY: The next question was about labial edema, and Dr. Peers will speak to that.

DR. PEERS: Yes. This is a slide which is

taken from our --

DR. NOLLER: Can't hear you.

DR. PEERS: Sorry. This is a slide taken from our clinical report where we had a demonstration of labial edema, and this is the Adept patients. I apologize if it's rather small. Is there any difficulty in any member of the panel seeing that? Is that all right? Thank you. So this is the adverse event recorded by the investigators. These are the words used by the investigator that he wrote in the case record form, and we put them all together and considered all these to be labial swelling. And then at the bottom here, the same but for vaginal, vaginal fullness, vaginal swelling, and vaginal vulvar swelling, so he considered those together with these in one table here.

And here we can see when the adverse event started, so you can see that pretty much all of those, with the exception of this one, starts within a day or two of surgery, and so certainly coincident in time which suggests some kind of relationship. And here we see the duration of the event, so you can see, again,

the majority, though by no means all, in terms of labial swelling resolve within one, two, or three days, with the exception of these two. In the case of this one, these were resolved, it was moderate. In the case of the one that lasted 41 days, this was mild. And then vaginal swelling and vulvar vaginal swelling here, lasting, again, a few days, and all of which resolved and were mild. The difference here, this one which started 30 days later, no explanation for this. It remained unresolved and was severe. I do not know whether that was a truly related event, but that's how we have reported it. Any clarification?

DR. NOLLER: Dr. Snyder.

DR. PEERS: Thank you.

DR. SNYDER: Originally, there were 13 cases of vulvar edema, and you attributed eight as possibly related to the Adept. I mean, what were the other five cases, I mean, because I count eight up there.

DR. PEERS: Yes. The 13 refers to the entire data set here.

DR. SNYDER: Okay.

DR. PEERS: Including the vaginal and vulvar swelling, as well. I should say here that in no case was there any evidence of ulceration, in no case was any surgical intervention required, and there was no drainage or anything like that required for these patients.

DR. NOLLER: Dr. Sharp.

DR. SHARP: My original intent of the question was really how much clinical significance do we put to this labial edema. And I was wondering whether the patients had to be re-admitted for inability to void, whether we can attribute it to the edema.

DR. PEERS: Yes. Thank you for clarification. Absolutely not. There was no such evidence that any patients were re-admitted. There would have been serious adverse events if that had been the case, but I would like to invite Dr. Luciano to comment specifically on that issue. Thank you, Dr. Luciano.

DR. LUCIANO: Thank you. It's actually

not that rare to see that, whether you use Adept or Ringers lactate. And it's usually a mild process that goes away very quickly. And, in fact, I know you cannot see that, but if you look at some of the patients who reported labial edema for a long time, the quality or the severity of it was usually mild, which is really minimal change that you could barely see, that you could barely notice it clinically, so it was really insignificant.

DR. SNYDER: Is there any hallmark of labial edema that would be arising from Adept that would be different from anything else? I mean, there's an excess of 5-1 of the unrelated on the --

DR. LUCIANO: I don't think so. It's really related to the volume of fluid that you leave inside. And the second determinant is actually the opening of the canal of nuc, where the Rowe ligament goes into the angular ring, sometimes that closed, most of the time it's closed, sometimes it minimally opens, but if it is open, then the fluid will travel down into the labia, so it's more of the function of the quantity of fluid and also the opening of the

canal.

DR. SNYDER: So really, we have no a priori reason to believe that the five that you haven't reported up here are any different from the eight that you have.

DR. NOLLER: It's not clear.

DR. diZEGERA: I apologize. There seems to be some confusion about the 13. And Dr. Snyder is correct about the 13, and if you add the top eight and the bottom five, you have 13. And when Dr. Peers presented that slide, the construction of the slide included both labial edema and vaginal swelling, and those are the 13, so it's the same 13. The reason that this was done was exactly as the point that you made, and that is, we think it's a fundamental demonstration of the same biology. It's retention of fluid inside the peritoneal cavity, as Dr. Luciano said, for a large amount of fluid for a period of time, and those individuals have a patent canal of nuc. These kinds of things can happen.

We had the same exact experience in the Hyscon studies, if anybody remember those Hyscon

studies back 20 years ago, a transient labial edema in about 5 percent of the patients, no specific therapy was warranted. They were all self-contained. And I should point out that sponsor does absolutely intent to include this on label.

MS. CLISBY: Dr. Corrado has one related comment.

DR. CAREY-CORRADO: Yes. This relates to the issue of whether there was any case of inability to void in association with labial swelling. There's one case kind of maybe a little bit nit-picky, but I do want to point out that in Patient 637 at Site 13, that's in your list of serious adverse events. That patient was re-admitted the day of surgery for inability to void. She also had labial swelling, and so I just wanted to get the record straight, and maybe the company would like to comment on whether they think there's an association between those two events.

DR. PEERS: Thank you, Dr. Corrado. We have the SAE report for this patient available. And this is the SAE that I mentioned this morning in the list of all the SAEs, and it's probably difficult to

read, but as you say, the patient is re-admitted with inability to void and labial swelling, ecchymoses at port side, nausea, vomiting, and all these lasted only one to two days, that includes the labial swelling, and the inability to void was severe. That's why she's re-admitted, but everything else was moderate. The patient was discharged on the second day of hospitalization. I'll read the details for you.

"The patient was admitted on the day of surgery for inability to void. She was observed overnight with intermittent catheterization and developed ecchymoses, nausea and vomiting. She was discharged on the second day of hospitalization." So that describes that patient.

As you can see, the reported causality from the investigator was that this was unrelated, and the FDA opinion, which we would share, actually, is there's a possible relationship between the device, in this case Adept, and the events seen in the manner that was described by Dr. Corrado. Thank you.

DR. NOLLER: Dr. Miller.

DR. MILLER: I just wanted to take this

opportunity, since we're talking about this complication, to highlight the question I had asked earlier, which was, from the experience that we have from your other product, the Extraneal product, is this something that's frequently seen in the use of that product as another peritoneal fluid?

DR. BROWN: Colin Brown. Thank you very much for that question. The interesting thing is that in peritoneal dialysis where there's a constant much larger volume all the time, the most common problem that we tend to see is in males rather than females. And it probably goes down the same anatomical tract, and they get swelling of the testicles on one side, as opposed to both sides. Scrotum, I mean scrotum. I'm a nephrologist, I work further upstream.

DR. MILLER: Thank you.

DR. BROWN: So I have to say clinically I've not seen this, and I've not seen it reported in the literature, although I haven't done a complete literature search, so you sometimes get fluid coming down to the scrotum. It requires suturing, and we keep these people on peritoneal dialysis. And while

I'm up here, sir, I think you also asked a question -- if I can just come to it -- was the safety issues. I think you also asked that question. Is that right? You also asked a question later about were there any safety issues that we could have learned from, from 7.5 percent Icodextrin Extraneal and peritoneal dialysis, and the answer is we have this greater than 75,000 patient years experience with 7.5 Icodextrin. There, obviously, overnight, every night for weeks, and months and years, and all we can say is that these safety issues are reported. There's nothing extra to tell us about any more than what we've seen with Adept. There's nothing unusually different in those patients. Does that answer your question?

DR. MILLER: Yes.

DR. BROWN: Thank you.

DR. NOLLER: Next question, please.

MS. CLISBY: The next question related to the irrigant that was used and whether or not it was aspirated from the peritoneal cavity. Dr. Martin.

DR. MARTIN: Let me answer it once and then make sure I've got the question right. Patients

were in Trandelenberg position. In that position, the cul-de-sac will hold 20 to 80 ccs of fluid before it spills out and goes into the upper abdomen. That part of the irrigant that was placed in and was within the cul-de-sac was aspirated out pretty much as we put it in, because it was used as a cleaning, irrigation solution throughout the entire procedure. That part of the solution that went over the pelvic brim into the upper abdomen was outside of the areas being evaluated, but at the end of the procedure we would reverse the patient, bring all the solution back into the deep pelvis, aspirate from the deep pelvis, and then flatten them out and put in the 1,000 ccs.

DR. NOLLER: Great. Thank you. That answers that.

MS. CLISBY: I think the next question is also for Professor Brown. There was a question about volume of fluid remaining in the abdomen. I think it might have been Dr. Miller's question, actually.

DR. CAREY-CORRADO: That was really just answered, I think, wasn't it? Or do you mean over time, that was the question.

MS. CLISBY: Over time, yes.

DR. CAREY-CORRADO: Yes. How long does it survive in the abdomen?

MS. CLISBY: Shall we go to a different question?

DR. NOLLER: No, that's fine.

MS. CLISBY: Okay.

DR. BROWN: Thank you. As you can see from this slide behind you, sir, is we want -- I think the question, if I'm correct in saying was, was there any influx of fluid within the peritoneal cavity, and this, I think, probably addresses that. This is 4 percent Icodextrin, instilled once with 2 liters, and you don't see any increase in fluid over the period of time. However, as you probably remember, I'm a nephrologist, and in renal disease, we use 7.5 percent in order to do exactly what you're thinking this might do in order to remove fluid from patients who have renal failure and can't pass urine. And that's the reason why we use a much lower concentration, because we don't want to draw fluid into the peritoneal cavity. What we want to try and maintain is a similar

volume decreasing over time within the peritoneal cavity.

DR. MILLER: But you instill one liter.

DR. BROWN: Correct.

DR. MILLER: And yet you have two liters.

DR. BROWN: This is the only experiment we could have done clinically. This is very difficult to get this sort of information, obviously, in the patient group that we've studied, because how do we find out how much fluid is in the peritoneal cavity after laparoscopic surgery leaving fluid in. Ultrasonography is not very accurate in finding that out, even transvaginal ultrasonography. The reason why I've shown you this slide is this is the only place that we've been able to get this data. This was a trial using IP chemotherapy for people with colon cancer, and between the times of having IP chemotherapy we wanted to maintain fluid within the peritoneal cavity, partly because possibly adhesions developing as a result of the inflammatory response to the 5-fluorouracil, so we were deliberately giving more than a liter, we were giving them two liters.

And in order to get their approval, they wanted to have the same fluid that they were having between their episodes of IP chemo, because we continued to give them fluid, keep their abdomen full.

DR. MILLER: So if I understand this correctly, at 4 percent you feel like it doesn't draw any extra fluid in, 7 percent it does.

DR. BROWN: Correct.

DR. MILLER: And then there was one of the early studies where you looked at like less than 2 percent or something like that.

DR. BROWN: Correct.

DR. MILLER: And, actually, it did not hang around as long, as well.

DR. BROWN: That question I can answer, unless you want Cathy Rogers to answer. That was in our animal work. We looked at 2.5 percent, 4 percent, 7.5 percent, 10 percent, and 20 percent to look at adhesion reduction, and we found that in the animal studies, it was the 4 percent that was just as good as 7.5, 10, and 20, but less than 4 percent we didn't get the same results, we got not as good results, and

that's why we use the 4 percent.

DR. NOLLER: Thank you. Next question, please.

MS. CLISBY: The next question was about Elizabeth's slides of the 10 most common A&Es.

DR. PEERS: Thank you. Yes, this is, as Lorna says, our top 10 most common adverse events between surgeries. And I think the question related to whether the reporting of adverse events in the Adept group and the Ringers group were statistically tested, and the answer is yes, they were all statistically tested, and none of them were statistically significant. Is that sufficient? Thank you.

DR. NOLLER: Thank you.

MS. CLISBY: The next question related to stratification so I invite Alison Scrimgeour to answer that one.

DR. SCRIMGEOUR: The two groups, the randomization was not stratified by any patient characteristics, but we did stratify by center. The supplies were sent out in blocks of six. Does that

answer the question?

DR. MILLER: Yes.

MS. CLISBY: The next question was about labial edema and inability to void, which we dealt with. The next one was about safety data on Extraneal, which we've dealt with. The next question related to data on inclusion of the irrigant which we used, which I'll hand over to Professor diZegera to answer.

DR. diZEGERA: Thank you. The two component concept that we think is important from the standpoint of maximizing clinical outcome in patients undergoing this type of surgery was derivative of studies, both animal studies and human studies, generated by others. Those studies showed that frequent irrigation with a balanced solution that had the ability absorb hydrogen ions and was isosmotic, that would very likely reduce adhesions. The data weren't compelling, but they were certainly directional, and so we did an animal study to look at this more specifically, and what you have on the left-hand side or the instillate-only data and then here

instillate is added to the irrigation. The animal model was New Zealand white rabbit. These rabbits are ten rabbits per group. They underwent what's referred to as a double uterine horn traumatization where the serosal surfaces of the uterine horns are braided until punctate bleeding develops and then collateral blood supply is removed. And they're very active in terms of generated adhesions to the control, so what we're looking at here are the percent adhesion-free sites. And you can see with instillation only at the end of the operation, this is a seven-day second look in these animals. You can see there is a very nice benefit with Adept compared to LRS. And I might say, if we had controls on here, they would be essentially down in this level.

And then we added the irrigation step and you can see that both LRS and Adept had additional benefits that we thought were important, and so moving forward into our clinical trial, we wanted to generate a treatment regime that would maximize the benefit of the patients, and made sense on a clinical/surgical basis.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: Yes. I appreciate that response. I guess I'm specifically saying, though, yes, that data does show value to using a combination of an irrigant plus the instillate, but it doesn't say that there's an advantage to using the Adept for both, versus using just Lactated Ringers as the irrigant, and using Adept as the instillate. There's no --

DR. diZEGERA: Right. If I understand your question correctly, with a two-component concept of what we're trying to do here with the irrigation component, as long as the debris and the clots that occur during surgery as aspirated and removed on a regular basis for something that's isotonic, and something that has the ability to absorb hydrogen ions, we're unaware necessarily of any advantage one over the other. And I don't think we can even begin to -- we don't have the resolution to look at that, but we do think it's important on a going forward basis that we include this information in the instructions for you, so as we talk to physicians, we do stress the irrigation/aspiration, as well as the

instillation to maximize the benefit.

DR. NOLLER: Thank you. Next question. We asked a lot of questions.

MS. CLISBY: You did. The next question was about labeling and training necessary for investigators. I'll ask Dr. Martin to speak.

DR. MARTIN: Our understanding, since the numbers are European, is that the Europeans had no specific training. I can answer that to the United States experience. Do you want the United States answer?

DR. NOLLER: Sure.

DR. MARTIN: Yes. In the United States, the gynecologists who were trained and our residents who we are training are all trained in use of irrigator aspirators. There was no specific training past that point of what they receive in residency.

DR. NOLLER: Thank you.

MS. CLISBY: The next question was about uterine manipulations. Perhaps Dr. Luciano could answer.

DR. LUCIANO: As you probably have

gathered by now, most of these patients had fairly advanced disease, lots of adhesions, and in order to visualize the adhesions and be able to remove them, you really need to use a uterine manipulator, so uterine manipulators are used almost universally in operative laparoscopy. Certainly, we used it all the time, and from the reviewer's experience, as you reviewed other surgeons working on it, yes, they've all used uterine manipulators.

DR. ISAACSON: Mr. Chair, real quick. Tony, you can answer this maybe from the last question. Did you use anything specific to make sure the fluid did not leak out from the incision or the port sites? Was there any training as far as that was concerned?

DR. LUCIANO: That's a very good question. Thank you, Dr. Isaacson. We made sure that the punctures were closed adequately so that the fluid remained inside. There's always a possibility of some minor leakage, but most of the time these were well sealed punctures, and it was left inside.

DR. NOLLER: Thank you. Another question.

MS. CLISBY: The next question was for the FDA regarding the center effect.

DR. LI: Okay. This question is from Dr. Weeks. If I'm correct, he's asking for how much of the center effect was due to the small sample size. We can see that they're predominantly significant center effect for all those three co-primary endpoints. And it is stated in the protocol that if the interaction between the center and the treatment, the P value for the interaction term is less than 10 percent than the interaction term would be included in the analyses. But if it's above 10 percent, we would drop this interaction term. And it turned out that the P value for the interaction term is bigger than 10 percent, so we only included the center factor in the primary analysis, so the center effect was adjusted. Does this answer your question?

DR. NOLLER: So you did adjust for center effect.

DR. LI: Yes.

DR. NOLLER: Thank you.

DR. EMERSON: But in terms of reporting

the additive difference, you did not adjust for the center effect. Is that true?

DR. LI: Can you repeat the question?

DR. EMERSON: So when we're looking at the difference in proportion and the confidence interval for the difference in proportion, it was not adjusted for the center effect.

DR. LI: Actually, the sponsor did both analyses. One is they included the center effect, the other one they didn't include the center. Then the two analyses gave very similar results. The results are almost the same.

DR. EMERSON: But the confidence interval you're quoting is the one from the unadjusted analysis.

DR. LI: Yes.

DR. NOLLER: Thank you.

MS. CLISBY: The next question related to those patients who had two diagnoses, for example, adhesions plus endometriosis, or adhesions only. Dr. diZegera.

DR. diZEGERA: I think this was Dr.

Chegini's question, and we have a slide that actually displays that data. I highlighted some of this earlier, and I apologize, Dr. Chegini, that I didn't highlight the rest of it. This is the patients that all had second look laparoscopy, and we're looking now at success, and success defined as we talked earlier. And we're talking about now the patients that had endometriosis, and the patients that did not have endometriosis, and see what difference that made. On the left-hand side are the patients with no endometriosis. On the right-hand side are patients with endometriosis in the categories that I described earlier. And so you can see an absence of endometriosis, so all these patients had adhesions that at first operation they had no endometriosis. You can see the treatment effect is essentially 15 percent. And then with endometriosis, we talked about that, more endometriosis, more treatment effect. Does that answer your question?

DR. CHEGINI: Yes, absolutely. The reason I asked the question, particularly after that, I realized that the intent in the previous slide you

showed, they were over -- I think it's from the European studies -- that over 920 patients that had endometriosis, over 1,200 had pelvic pain. I forgot, I didn't write down, but quite a considerable number, they also had reduction in lyomyoma. And as you know, I really don't have to say that one at all, but almost every one of these patients are because of infertility. And so, therefore, when you apply this material and the endpoint and the term of birth rate was lower, I was just questioning in terms of if this was targeted mostly toward that group versus the one that have generally adhesion and they are not going under infertility.

DR. diZEGERA: Right. And I can just quote Dr. Corrado, there was never any adjustment, never any inclusion criteria, never any evaluation to even begin to ask the question about infertility. That's a very, very different study with many complexities, and that's why we don't really report the infertility data. We don't have any hard evidence that Icodextrin effects ovulation, or fertilization, or implantation, or anything. And I think you also

asked a question about glucose in the peritoneal cavity. Icodextrin does not contain glucose, so there would be no glucose in the peritoneal cavity.

MS. CLISBY: The next question was in relation to the scoring sheet and how it was derived. Dr. diZegera. And Dr. Luciano will speak to how it was completed.

DR. diZEGERA: I'm not sure which of us has the easier task here, Dr. Isaacson. The scoring sheet -- actually, if we went back 20 years ago and I showed you the scoring sheet we used for Intracede, you can see how these things have progressed over the years, and it just becomes more and more complex. And I think like most fields of medicine, the more we know about it, the more we become splitters, not so much lumpers in terms of getting specific information to drive clinical impressions. And so this scoring sheet represents basically everything that we thought would be useful from the standpoint of understanding an adhesion reduction device that had a long intraperitoneal dwell time, and where it would have clinical benefit. And so we captured 23 different

anatomical sites, and these anatomical sites include adnexal sites, they include anterior abdominal wall, lateral pelvic sidewall, small bowel, large bowel, and so forth. And with a fluid, the idea was to see if we could get a generalized peritoneal reduction or was there a reduction isolated to one or other part of the pelvis. And, in fact, there was a generalized reduction.

We're able to show more statistical power with the adnexal areas because of the AFS score, which specifically addresses that, and that would have been on the back of this sheet, so many anatomical sites. If were looking at a site-specific barrier, we'd only have one anatomical site. Here we're looking at a large number.

And then in terms of the different types of adhesions, and I should say the severity and the extent issues, we're now talking about one, adhesions that might be vascularized, and we all know full well the difference between vascularized adhesions and non-vascularized adhesions in terms of the surgical requirements of their removal, and the likelihood of

their reformation, so we wanted to capture that information. And then, of course, the last thing that I think is a very important addition to the study is the endometriosis. And, frankly, I think we were a bit surprised at the number of patients that actually had endometriosis. As we found out, it was actually two-thirds, and that wasn't any specific inclusion criteria. That's the way it turned out. And the distribution of the endometriosis across the anatomical sites was exactly as we all learned in medical school, the adnexa, the cul-de-sac, and so forth. So the idea was to get as much information as we could in a reasonable time period by the surgeon at the table doing the procedure. And so what I'd like to do now is --

DR. ISAACSON: Before you go, where are the data on vascularization of the adhesions? I haven't seen that presented.

DR. diZEGERA: That relates to the severe versus the filmy, and that's built into the AFS scoring system.

DR. ISAACSON: So the dense adhesion is by

definition vascular?

DR. diZEGERA: The dense adhesion would be vascular.

DR. ISAACSON: And then tell me, because you had the modified AFS score, as well, which was not statistically different. What part of this between the AFS and the modified AFS gave the statistical difference?

DR. diZEGERA: That's a very insightful question. Just so we're all clear about the terminology. The AFS score was the one that was developed in 1988. The modified AFS was something that myself and others in this audience brought forward a few years ago, and the idea was to use the two points that you just talked about, the severity and the extent, as are used in AFS score for the ovary and the tube. Take those two parameters and extrapolate them to other anatomical sites. So, for instance, the lateral pelvic sidewall, extent and severity; the intrauterus, extent and severity, so it's just using those two clinically derived observations at each of the 23 anatomical sites.

That's what the modified AFS score is. And I'm sorry, what was your other question?

DR. ISAACSON: But the modified I think there was not a statistical difference of the two, but yet it was in the AFS in the infertility group, per se.

DR. diZEGERA: Right. I think the issue there relates to the amount of adhesions we had to test for. As you recall, this was adhesiolysis study, so there had to be adhesions removed. And in this population, there were a lot of adnexal adhesions, and so that gave us a chance to evaluate the effectiveness of the device. It's hard to show a benefit when there isn't much to challenge it with, so you can imagine there weren't a lot of bowel adhesions, et cetera. But the adnexa were the focus, and that's why I think the AFS score really is a better way to go forward with these kinds of evaluations.

DR. NOLLER: Thank you.

DR. ISAACSON: Thank you.

DR. ROMERO: May I ask an additional question about the completion of the questionnaire?

You're doing this interoperatively?

DR. LUCIANO: Yes.

DR. ROMERO: And so you're dictating this to someone who is transcribing that.

DR. LUCIANO: That's correct, yes. And that's to answer your question, which was an excellent question; that is, when do we fill out the score of these forms, and we did it interoperatively. We had my research assistant, and that's part of the protocol, and every investigator did the same thing. The research associate would read us each of those 23 sites, and we would say yes or no. If there is an adhesion, then she would ask us the severity of the adhesion, and whether it was vascular or filmy, et cetera, and that score will be filled out at that time. Sometimes if a surface was not available, she would wait until we exposed the surface before we score it, and it would be done at the same time.

DR. NOLLER: Thank you. Another question.

MS. CLISBY: The final question related to the labeling and the incidence that you quoted, the 28 percent of adverse events in the Aerial Registry.

That 28 percent occurred, the reporting rate was in the general surgical laparotomy, so that probably will have included more surgeries that were not clean. But we have included in the proposal labeling for Adept two statements in relation to that, which say the safety and effectiveness of Adept has not been evaluated in clinical studies in the presence of rank infections in the abdominal pelvic cavity. And also, that the safety of Adept has not been established after unintentional enterotomy or bowel perforation, so we've tried to cover a precautionary statement.

DR. NOLLER: Thank you. Very nice job.

MS. CLISBY: That concludes the questions, but could I just ask whether we have really covered all of your questions on blinding and video audit?

DR. NOLLER: Please have a seat and I'll take care of that next. Now just to alert people, if there is anyone here for a second open public hearing that wants to make a statement, we're running about an hour and 15 minutes behind time, so it will be quite a bit later than the 4:15 time. And I would guess our deliberation votes will be more like 7 p.m., something

like that. So at this point, now that we've had those questions answered, we'll see if there are any other questions. At the end of that question and answer period, we will then as a panel begin our discussion of the FDA questions. That's expected to take approximately two hours. So do we have any more questions either for the sponsor or the FDA at this point? I want to make sure all our questions are answered. Yes, Dr. Romero.

DR. ROMERO: Yes. I had a question for the FDA. I was interested to maybe get a deeper explanation as to why we were presented with the pregnancy outcomes data. That's not data that the sponsor discussed at all, and I think when the conversation turns to clinical significance, the findings of the endpoints, because there's a particular interest on the infertility data, the secondary endpoints that deal with infertility, I'm struggling right now with whether I should even pay attention to the pregnancy outcomes data that the FDA has available.

DR. NOLLER: FDA, you want to respond why

did you bring up an issue the sponsor didn't raise?

DR. CAREY-CORRADO: The first thing that I would say is that pregnancy outcomes was discussed at the 2001 closed panel meeting as an obviously meaningful clinical endpoint. However, the panel agreed that it wasn't practical to design a clinical trial, a pivotal clinical trial to look at that as a primary endpoint. Nevertheless, at that time the panel said that it's an important outcome, and it would be worth pursuing potentially post market depending on how the pivotal trial went.

I certainly agree that the sponsor has not tried to introduce that data as effectiveness data. Nevertheless, the PMA includes pregnancy outcomes data in the response to one of our questions that we sent out in July. There is a section of the PMA that talks about the SALLY Registry, and that was pregnancy outcomes in the two groups. The sponsor has been very up front that they do not know which patients received IVF, and so, therefore, I thought it was fair to include it in the presentation to kind of connect the dots between the 2001 meeting and this meeting, at the

very minimum.

DR. NOLLER: Thank you. Other questions from panel? Dr. Miller.

DR. MILLER: Yes, before you go away from the podium, can I ask you to revisit the issue of the 5 percent threshold in light of what the sponsor's response was? I just keep coming back to the fact that now in retrospect, is it possible that that 5 percent was an unnecessarily high threshold that the FDA on reflection of these results would agree was not really necessary. I mean, we all like to believe that when we're constructing trials that we construct them with the best information, but sometimes we realize in retrospect that some of our a priori assumptions were not the best assumptions, and I want to know what your thoughts are as to how we should think about that.

DR. NOLLER: I looks like Mr. Pollard wants to answer this one.

MR. POLLARD: Yes, thanks very much. And, in fact, I think -- I want to just kind of really turn that question right around to the panel. The hypothesis is what it is. I think it was negotiated

in good faith at the time. We were trying to set a mark that we thought would really at the end of the day if it hit all three on all three marks, that we would really feel good about things. Did we set it too high? I think that's, in fact, one of the things you're going to have to grapple with when you deal with question one.

We can go into all the details of how we got to that point, and I might disagree with one of the previous speakers that I think there was a lot of good thought that went into it. At the same time, you've got the data that you've got in front of you, and I think I'll probably leave it there.

DR. NOLLER: Dr. Emerson.

DR. EMERSON: Just a follow-up there. Two things that were going through my mind would be whether this was, perhaps, due to the surrogacy of this endpoint relative to what mattered. And then the other question is whether it's a pivotal trial. Did either of those come into play here?

MR. POLLARD: I would say it was a constellation of factors, and those certainly were a

couple of them. Again, I don't think we can probably shed any more light on it than you've heard already this morning, and that's why in my opening remarks I said it's going to be a little bit of a challenge for you to grind through that data and see if you want to look past the hypothesis, and if you do, whether or not the findings there represent a clinically significant result.

DR. NOLLER: Dr. Hillard.

DR. HILLARD: Just a question in terms of the background discussion about the use of Lactated Ringers for controls. It looks to me as if one of the conclusions is that Lactated Ringers works reasonably well.

MR. POLLARD: Sounds like something you might want to discuss.

DR. NOLLER: Other questions before we start our deliberations. Dr. Snyder.

DR. SNYDER: Yes, I still have the one question. Somewhere going through all this, I was left with the conclusion that there's still, even though you've got a lot of the absorption data and

look at the metabolism and you know what the renal clearance is, but there's still a lot of individual variation for any individual patient in the rate of absorption. Is there anything in the use of the 7.5 percent data or anything that tells us a way to decide how long that that increased peritoneal fluid is going to be there, because if your hypothesis is that you need something that is going to extend out for 72-96 hours or whatever, that there are patients who do absorb this in a faster fashion than that time frame, and it just seems to me like that could affect the outcome depending on which patients absorb this faster.

DR. NOLLER: Sponsor want to respond?

DR. BROWN: The answer to your question is I can't give you a precise answer for very obvious reasons, because the only way we could collect absolutely direct clinical information is that slide I showed you on the volume slide. There is no other way that you could do this ethically; for example, putting radio labeled albumen into the abdominal cavity of a patient after gynecological laparoscopic surgery, and

aspirated, and measure what the residual volume is, which is what we do in peritoneal dialysis. But then we have the opportunity to do that, because we've got an in-dwelling catheter in there as part of their treatment.

I can only draw your attention to the error bars here, sir, and here, and here, which for this particular group of patients, and I can only speak to this particular group of patients, doesn't seem to be very wide, to suggest that there's a lot of variation. That's the honest answer.

DR. SNYDER: And I agreed with your conclusion earlier that ultrasound imaging isn't a good way to really quantify amount of interperitoneal fluid, although it is a great way to tell whether there is presence of fluid or not, and so if you did daily transvaginal ultrasound you could tell when you've got less than 30 ccs of fluid in there.

DR. BROWN: You're right. And we didn't do that in this study. A study to do that has been tried, and I might turn to my colleague, Professor diZegera. Do you know if that study down out of

Hammersmith was -- the study was tried. In fact, we discussed with the gynecologists at the Hammersmith Hospital at Imperial College in London, and they were going to do exactly what you described. It wasn't, for reasons I don't know because I wasn't involved in it, it was terminated shortly after starting it. My understanding was there were problems actually assessing the changes in volume over time, it was so variable. And the other problem was, of course, getting patients approval to do this, which wasn't in their clinical interest, so I'm sorry I can't give you a perfect answer.

DR. NOLLER: Thank you. I didn't see any other hands. Are we ready to go to our discussion? At this point, this will be a discussion among the panel members ourselves. FDA and sponsor will not come to the podium unless you're invited by me to do so. If you think you have a terribly important point to make, something that we are clearly considering incorrectly, please raise your hand, and at the appropriate time I'll ask you to set us straight.

If the panel would pull out of their blue

folder the panel discussion questions, and is it possible to put the FDA's presentation question there? Those were nicely summarized. Now I'm not going to read the whole question, as we've gone over all of this so much today. The first question revolves around the three co-primary endpoints of individual patients' success, mean change in sites with adhesions, and consideration of the dense adhesions. We're going to take each of these in turn, and we're going to talk about the objective, the statistical testing that was done, and the clinical significance. And the first will be the first co-primary endpoint, the individual patient success. And in the pivotal study table you have there, you can see the actual numbers.

Remember that in the Adept arm, about 45 percent had a reduction, and in the Lactated Ringers arm about 35 percent had a reduction, so who would like to speak to objective statistical tests and clinical significance of this first primary, co-primary objective? And please raise your hand as you -- I seem to be getting a message from FDA. Oh, I

thought you wanted to say something. Okay. Dr. Isaacson.

DR. ISAACSON: Well, this strikes me almost as a summary statement that there's very -- two distinct differences between statistical significance and clinical significance, and that keeps coming up throughout the whole day in my own mind.

I think the clinical significance more related to question two is very real. I think if you ask me ahead of time do I think 10 percent or 9.8 percent difference between what was supposed to be a placebo and a product, is that clinically significant, I would have said no. But it certainly is clear that I think it is statistically significant, and I agree with the sponsor that the 5 percent bar in retrospect probably didn't make a lot of sense to me. So my statement is I definitely think it's reached statistical significance, which I think is important. But I'm not as convinced that 9.8 percent difference between the two arms is clinically significant.

DR. NOLLER: Yes.

DR. SHARTS-HOPKO: I look at that in kind

of the opposite way. We didn't do well on the statistical differentiation, but we've taken a product which is not a product for this purpose. It was the best choice that people could come up with for a yardstick of comparison, and much to everybody's shock and dismay, it turned out better than anticipated. But we're comparing the only product around with a substance, the control substance which is not a product for this use, and we get somewhat compelling clinical outcome data to support the placebo, but I think you have to put that aside.

DR. ISAACSON: But I think we have to not look at it as a placebo.

DR. NOLLER: Dr. Emerson.

DR. EMERSON: I have some sympathy for not looking at it as a placebo, and then I have some sympathy for the fact that if you take the placebo arm with most clinical trials right as soon as the investigators know that you've stopped the run-in, you'll see a difference on the placebo arm, as well. And so I worry very much about this, everything being assessed in a completely unblinded fashion. That's

the reason why we have the other arm, is to say is there a possibility that maybe the investigators believed the treatment was really going to work a whole, whole lot, and then they applied it indiscriminately on the two arms, so I have some problem with that, although there's still this concept of it might be active in some element of the presumed mechanism of action, just the volume could having an effect, so I have some sympathy for that.

As far as the statistical significance, I'll just note that the P value that's being quoted doesn't match the confidence interval that's being quoted for the difference, that if you get the confidence interval that matches the P value that's being quoted, it's a confidence interval that runs roughly 2 percent to 18 percent, rather than the 1 percent, so that adjusting for the center adjusted for apparently some imbalances by center where there was a strong effect, so that's also moving it more towards having a little bit of sympathy.

In terms of the 5 percent threshold, however, again the two things that I can imagine; one

is, it's not uncommon when only one clinical trial, well-controlled clinical trial is going to be presented that the FDA and other regulatory agencies might like this to be regarded as a pivotal study, so rather than having two studies, they'll take one, but it has to be stronger evidence. Numbers are pulled out of the air, but something along the lines of a .01 significance level for that pivotal study, so it's not to the .001, although sometimes I quoted that, but there's arguments can be made to .000625, I mean, so this concept of saying it's not completely unheard of to put this greater burden on a single study, and then the surrogacy endpoint. It's this idea of saying if you don't have the real endpoint and you ask the pregnancy question, which I also wanted to know, because that's a very important thing; that if we're thinking that this is sort of lukewarm endpoint, and by the time we've dichotomized it, perhaps at the wrong level, perhaps just having 10 percent fewer adhesions isn't what you need, maybe you need 25 percent fewer, or 50 percent fewer, or 100 percent fewer before it starts mattering. And so I, probably

like everyone else at the table, was first saying well, why have that 5 percent threshold? And I'm not certain that we have to. It would be far more likely that I would have not expressed it as the 5 percent difference. I would have expressed it as how confident we have to be in these results, but these are the things.

I feel relatively confident that we've demonstrated that there can be fewer adhesions. I'm just not yet certain what that means.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: I'm just a simple person from Texas, and I understand both what you were saying and what Dr. Isaacson was saying, but I guess the way I look at this is, when in the best of intentions when this panel got together in 2001, whenever it was, when they set the rigidity of trying to meet all three of these primary outcome measures, it was with the assumption that they were comparing it against a placebo. And then lo and behold, we got some scientific evidence that shows that it probably wasn't exactly compared to a placebo. But then on top of

that, we have some good statistical data that says that it does decrease the absolute number of adhesions in a given patient. And I think that to back-off of what that original intent of the committee was or the standards that they set, it has to be factored in that this is a little bit more complicated than maybe the straightforward comparison to placebo.

DR. NOLLER: Dr. Cedars.

DR. CEDARS: I think the issue in terms of do we count this as a placebo or not count this as a placebo, I think given the way that the scores were read by the primary surgeon. We knew they did a surgery, and we knew they did a second surgery. If you didn't have a "control" or a placebo, we all think we do great things when we're in the operating room, and so I think you have to have some parameter by which to judge your "improvement." If you're not going to take these videos and read them in a blinded fashion in a random, not knowing which is first and which is second, if your way that you're assessing improvement is the surgeon knowing which is his first procedure and knowing which is his second, you have to

have some control for that, so I don't think you can take that out and say let's just look at what the agent did.

That being said, to say that this isn't a product that's approved for this purpose, we all have Lactated Ringers, we all irrigate as we do surgery, and so I think you really do have to have that as a threshold bar of where you are at baseline, and then you want to get something that's superior to that. Now how you want to define superiority, whether it's at that 5 percent level, or whether it's just statistically significant with a normal confidence interval that's above zero, that's open for debate. But I think you have to have some comparator that you can't throw out that other arm.

DR. NOLLER: Dr. Sharts-Hopko.

DR. SHARTS-HOPKO: The question that I have is, current standard of practice, is it to instill 1,000 ccs of something?

DR. NOLLER: No. One comment, and Dr. Emerson, I'd like to ask you about this -- when the study was designed, it was expected that there would

be about a 25 percent reduction in the placebo arm, and it turned out to be 35 percent, so it was -- the post placebo wasn't. Had it been 25 percent, it seems to me that we wouldn't be having this discussion. Is that correct?

DR. EMERSON: Well, if the placebo arm had 25 percent and the treatment arm had 35 percent, yes, we'd still --

DR. NOLLER: Forty-five.

DR. EMERSON: Well, is it fair to say that you're going to just change one of them?

DR. NOLLER: No.

DR. EMERSON: So at 25 and 35 it still would not have passed that bar, the confidence interval. You would have had more precision, but it wouldn't have been enough to pass that 5 percent bar. It's sort of like the comment that the sponsor sent back about saying to meet that 5 percent bar, we would have had to have -- rather, they stated with a sample size of 750, it would have been significant. And no, the answer is we were worried about with a sample size of 750 it might have been a different testament, as

well. And so this is this thing that we don't know what would happen.

DR. NOLLER: Other comments about the first part of the first question? Before we move on, does the Division Director have any comments? Have we helped out at all on this so far?

MS. BROGDON: I'm looking to the Branch Staff for the answer to that.

DR. EMERSON: Could I ask a question about this instead of coming back up?

DR. NOLLER: Sure.

DR. EMERSON: The rest of the panel, I mean everybody else in this room knows what AFS is, but not me.

DR. NOLLER: American Fertility Study.

DR. EMERSON: Yes, I could have told you that. I just couldn't tell you what it is. Is that a good surrogate? How comfortable do we feel with this measure of the adhesions as a surrogate? And one of the questions I have about the AFS is undoubtedly it was chosen as a good surrogate predicting in an unintervened state, so we take people who we haven't

treated and this might predict what their fertility might be. Do we know that modifying that, doing things to a patient that will change that score, that that will also translate into improved fertility?

DR. NOLLER: Dr. Isaacson, you could answer that, I bet.

DR. ISAACSON: There is where it comes into -- the answer to that is no, but with some qualifications. The qualification is certainly the greater the extent of the adhesions the more likely -- that's why the American Fertility Society came up with that -- the more likely that if you're going to have trouble with fertility, but it's not absolute and no one has said at this level there's a difference between a 10 percent, 20 percent, 30 percent, that that's going to yield higher pregnancy rates; though it's assumed that it probably does on some continuum. It gets back to what is clinical significance, and that's where there's no consensus as to whether it's 10 percent clinically significant, or it's 20 percent, or it's 35 percent.

DR. EMERSON: I was going one step further

because I'm even simpler, but not from Texas. The concept of we know that in cancer, if we compare people who have a tumor and people who don't have a tumor, the people who don't have a tumor survive better. But we also know that if we take people who have a tumor and we cut it out, quite often they don't survive back like the people who didn't have it before, so it's this question of we can have a perfectly good scale that's predicting in an observational status. And then we intervene on it, and it turns out we were treating the symptom but not the disease. How much is known about the AFS?

DR. NOLLER: I might just say, that has been the standard method of counting or prescribing since `88, and a lot of papers have been written about it. But when it was devised, it wasn't a prospective evaluation. It was a bunch of people sitting around a room and saying let's figure out some way to count these things. Did you have a comment?

DR. CHEGINI: Yes, that's exactly what I was saying. I think it is highly subjective, and it depends on individuals. One extensive adhesion may be

small to one and severe to another one; so, therefore -- and there is also no data, in my opinion -- if anybody knows, correct me -- that the rate of fertility would change if you reduce it from extensive to a mild. A patient with mild adhesion could have severe inflammation and not have any outcome of success with pregnancy, so that's why the question came back for the length of time that they have the study, this one. It was only a month or two, so the targeted populations were mostly infertility patients because they were going under that procedure in order to become pregnant.

DR. NOLLER: Let's remember, though, too, not to focus too much just on infertility because there are many, many women that have completed their family or don't want children, that have pain or other symptoms, and so fertility isn't the issue, so counting babies or only focusing on infertility isn't the only thing. Pain is also important, but fertility is important. Nancy, did you have a --

MS. BROGDON: We'll work with what we have.

DR. NOLLER: Oh, Dr. Cedars.

DR. CEDARS: One of the other comments I had is if you look at this just total score at the top, and then if we're going to talk about effect on pain, or fertility, or any other outcome. And granted, what we're looking at is just what we have, there's no difference in the dense adhesions on the second look. And if you think about what the severity of whether it's an AFS score, whether it's any other score, the severity of the adhesions and the more dense adhesions, the more likely the pathologic outcome. And so that, again, makes me feel a bit more like setting a more stringent criteria for the first endpoint, which is sort of everything all added together is not such a bad thing, because if, in fact, as the sponsor was stating, the more severe adhesions the better the agent does, then you would have expected that co-primary number three to show a difference, and you really didn't.

DR. NOLLER: Dr. Isaacson.

DR. ISAACSON: It kind of gets to the confusion that I had anyway when I read it about six

times, is what the definition of success was, because I would not say, and certainly this was going to come up later in one of my comments about their labeling -- it's very unclear to me, this is not a universal definition of success. And success was achieved with a number of sites with adhesions decreased by at least the larger of three sites or 30 percent of the number. Again, I read it again, and it's still not clear, so part of it is focusing a little too much in my mind on patient success. It sounds good, it's easy to talk about, but really what they're talking about is not a clinically utilized term frequently.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: I have a question that I want you all to help me figure out, because this is real germane to what Dr. Cedars was just saying. Now the question asked by Pivotal Study 3 just says "the absolute number of fewer dense adhesions in an established patient," but that doesn't necessarily correlate with the number and severity of adhesions. In other words, if there's already dense adhesions, there would be good reason to think that nothing is

going to affect whether those dense adhesions are going to reform or not, because there's vascularity or it's set out in everything.

DR. CEDARS: But I think that's what the agent is being purported to do. I mean, we have nothing -- I mean, the assumption is we have nothing at hand now, but that's what's being --

DR. NOLLER: Let me interject here. It isn't just dense adhesions we're to be looking at here. It's adhesions, dense, medium, light, few, so the whole panoply of adhesions is what they are suggesting is improved.

DR. SNYDER: So let me ask this question again. If you just look at question 3, it just assesses the number of few dense adhesions between the first surgery and the second surgery. But when you look at the secondary outcome points, and their data would suggest by AFS scores that there's even a more profound effect, it wasn't just looking at dense adhesions. It was looking at total number of adhesions. So again, I get to the point where there may be nothing that's ever going to cause fewer dense

adhesions, but there may be something that might prevent fewer total number of adhesions where there's already dense adhesions. Am I making any sense?

DR. NOLLER: Dr. Sharp, and then Dr. Cedars.

DR. SHARP: Just looking at this from a patient's perspective, and what is clinically relevant, I think a lot of times when we do surgery and there's a lot of literature to suggest we make adhesions, we do make it worse, and so I think I would certainly give some credence to a product that would at least diminish that expectation by a third as being clinically relevant, so I think if I were -- for example, if this didn't go to market and I had the option to put Lactated Ringers off-label, I might do it. I think it is actually clinically relevant if you look at what the natural progression of adhesions after surgery is.

DR. NOLLER: Dr. Cedars.

DR. CEDARS: Well, I was just going to say about the AFS scores, and maybe I'm remembering these numbers incorrectly, but the correlation in terms with

pregnancy outcome versus the ten and under, and the twenty and higher, or the ten -- if you looked at those scores, they actually, as I recall, were all in the ten and under to begin with. I mean, they sort of went from ten to eight. I would say how significant is it if goes from ten to eight? If you took somebody who had an AFS score of 22 and it went to 10, I'd feel like it was a lot more significant than to say it went from 10 to 8, or 10 to 7.

DR. NOLLER: Dr. Miller.

DR. MILLER: Yes. I want to complement what Dr. Sharp just said, because I feel like that's true. And again, these were women that were suffering in some way, so they have pain, they had endometriosis, they had infertility, they had complex pelvic pathology. We're looking at a product that may not have met all of the benchmarks in terms of success, but there is a trend across all of the analyses in one direction. Some are statistically significant, some aren't, but if I were a woman and I was having a laparoscopy and you told me that there was a product available that could reduce my adhesions

by 30 percent, or by three, I'd say yes, I want that stuff.

DR. NOLLER: Dr. Weeks and then Dr. Hillard.

DR. WEEKS: I guess I'll sort of be the dissenting opinion here on the last two speakers. I would, if I knew that filmy adhesions or moderate adhesions are going to cause me pain. So as I see this data, we have a reduction in total number of adhesions. It seems like most of that reduction is in the group with relatively mild adhesions. And the question from a clinical efficacy point of view is how much are filmy adhesions or moderate adhesions going to contribute to a patient's pain; endometriosis, in the long run, probably a reduction in filmy or moderate adhesions isn't going to make a clinical difference. So I think the clinical question is the key one. Statistically, I agree, there's pretty good evidence that the device moves things in the desired direction, but I'm having trouble accepting mild adhesions or moderate adhesions as something that really improve quality of life.

DR. NOLLER: Dr. Hillard.

DR. HILLARD: Following up on the perspective of the patient, I think that if the issue is put to me as a patient using a product that will reduce adhesions and possibly pain, possibly impact fertility, compared with using an agent that is used every day in surgery, maybe not instilling a liter of fluid, but something that is routinely used, and surgeons are well aware of its safety overall. The FDA is aware of its safety in allowing it to be used as a placebo. I think that one evaluates that differently in comparison to a placebo that had a good effect.

The other issue that I'm having trouble separating, again, simple from Ohio, is that I can't separate the safety and the efficacy. Again, the patient looking at the issue, if it's maybe going to have a little bit of a benefit over the placebo of Lactated Ringers, but is going to cause X, Y, and Z as potential side effects - how severe are those side effects, so I think that those issues are linked.

DR. NOLLER: Dr. Isaacson.

DR. ISAACSON: That brings up what I was going to speak about. And to me, I think this was an excellent double-blind study that's very difficult to do. I think the safety profile was very, very encouraging, in my mind, which actually lowers my threshold for needing to have significant clinical benefit. I think it's clear that I find the data very compelling that it's a very safe product; therefore, if there is a benefit, which apparently there is a statistical benefit, this trial was not designed to try to determine if there was a difference in quality of life, fertility, or pain. It was just designed, is there a statistical benefit, and I think there is.

DR. NOLLER: We will be taking up safety as a separate issue; but, of course, it is important in clinical significance, which is what we're supposed to be talking about here. We started with co-primary one, and we sort of morphed into three a little bit I have a feeling we should discuss two graphs at this time. Howard, did you have something to say before we start?

DR. SHARP: I was just going to talk about

three for a minute.

DR. NOLLER: Talk about three for a minute.

DR. SHARP: That was that I agree -- I think the dense adhesions are a real problem, no doubt. And again, the struggle is that the placebo seemed to work so well. And what number three kind of tells me is, if I'm reading this correctly, both the Adept and the placebo worked fairly well. I think the reduction is 50 percent.

DR. NOLLER: Yes, 50 versus 40. Right.

DR. SHARP: So there was no difference between those groups, but they both seem to have less dense adhesions on the second look.

DR. NOLLER: Yes.

DR. SHARP: So again, not a difference, but certainly treating with something seemed to benefit that outcome, which is probably one of the more important ones, which are the dense adhesions.

DR. NOLLER: Yes, Dr. Emerson.

DR. EMERSON: I just do want to point out that that's 50 percent people had a decline in the

number of adhesions. Now we call it a set of measures, zero, that it would be exactly the same number at two times, so that half the time it would be less than and half the time it would be more than, and to attach too much importance to that 50 percent as being: we're getting improvement, I think could be they're staying exactly the same.

DR. SHARTS-HOPKO: I wanted to respond to a comment that Dr. Weeks and Dr. Isaacson made about pain. You do have data that pain was substantially reduced, 80 percent, so you said you would maybe support it if you had some notion that there was pain attached. Well, we can't attach adhesion work to the pain work, but we do know that pain was reduced.

DR. NOLLER: Dr. Cedars.

DR. CEDARS: What pain data do we have? I mean, we had data at two months, but that was really just -- I don't --

DR. NOLLER: Which slide was --

DR. CEDARS: I don't know that there was any data on outcome, of pain as an outcome.

DR. NOLLER: Was a slide presented about

pain? I don't remember. This morning did you present a pain slide? Could we see the last summary slide, please. "Eighty percent of patients with pelvic pain had a reduction in pain," in which arm, your arm, both arms? Please answer at the podium. Thank you.

DR. diZEGERA: "Eighty percent of patients with pelvic pain had a reduction in pain," that was true in the group that received Adept, and as Dr. Cedars correctly pointed out, that was at two months. And the same thing essentially happened also in the Lactated Ringers group.

DR. NOLLER: Thank you.

DR. SHARTS-HOPKO: But you don't instill in normal surgeries.

DR. NOLLER: Thank you. Let's talk a little about co-primary two, the number of sites with adhesions. And that's just the Adept arm. Dr. Snyder.

DR. SNYDER: I agree with what Dr. Weeks said. I'm not sure, and I don't think anybody is, what the true clinical significance of adhesive disease is across the board, pain, fertility, or

whatever. But given the choice personally of whether I would rather have adhesions, or no adhesions, or less adhesions, I'd rather have less adhesions.

DR. NOLLER: Other comments? Dr. Weeks.

DR. WEEKS: I think that's true, depending on how much risk I have to expose myself to, and what kind of procedures. And the pain, most of the data on pelvic pain shows that the majority of patients respond very well to just about any kind of surgery, but by six months or a year you have essentially no residual effect. So I'm still uncertain about this reduction in filmy adhesions, and whether that's a true clinical victory.

DR. NOLLER: There was a reduction of about two and a half adhesions, is that important or not. Dr. Miller, you looked like you wanted to say something.

DR. MILLER: No, I was just going to say that it seems like the reason why we don't have much to say about point 2 is because it's probably the least controversial of the points. That was the one that they clearly hit their mark in, statistically

significant. It has all the frills of being good.

DR. NOLLER: Okay.

MS. BROGDON: Could the staff make a comment about the pain question?

DR. NOLLER: Yes, they certainly can, doctor. Mr. Pollard.

MR. POLLARD: I really don't want to -- or maybe I can't -- find slide number 46 from our presentation this morning. I just wanted to -- and maybe Dr. diZegera wants to comment after -- but we put up the slide under adverse events for pain. It was actually measured three different ways. There was post op pain, there was pelvic pain, there was abdominal pain, and then comparing it between the Adept and the Lactated Ringers arm. And Dr. diZegera just pointed to that one bullet from their last slide, and we were trying to correspond that to our own three markers of it. And it looked like that was looking at post op pain.

DR. NOLLER: Those are adverse events.

MR. POLLARD: Right. And I'm not sure you were talking about post op pain, so I just wanted to

make sure we're looking at apples, and not oranges kind of thing.

DR. NOLLER: Yes. Dr. Emerson.

DR. EMERSON: I just want to return to Dr. Miller's comment. He may not be talking about point 2 because he feels it's so clear. I'm not talking about it because I think it's sort of irrelevant that in the unblinded assessment of that change, I just don't know how to look at that. Although, I will note that you have the P value of .047 between the two groups, and that counts more to me than it does the within comparison.

DR. NOLLER: Let me summarize a bit. I'm not hearing anybody say they don't believe the study results. We haven't called into question the methods. There are always ways that we might have done it a little bit differently, but we think it was a well done study. Double blind studies, including surgery, are very hard to do, and it was well done, the data fairly presented. We're struggling I think mostly on what's the clinical significance. There is a difference. Adept is better than Lactated Ringers it

looks like, but is that difference enough to matter? And that, I would guess, is about where we are. Is that more or less how far we've come? Because if so, we could talk about the second question, because we don't have to make any decisions just yet. Fair enough? Fair enough. Let's go to second question.

The second question we're asked to focus on the second area endpoints. And you remember a lot of different endpoints were looked at, and we're supposed to discuss the statistical and clinical significance of the secondary outcomes, in particular focus on the data for subjects with a primary diagnosis of infertility. Anyone want to start that discussion? We have a table pivotal study under Question 2, page 2 of our handout. Dr. Emerson.

DR. EMERSON: Again, this is just addressing it first with a question. Is there any reason to pre-suppose that this treatment would work better in patients who have adhesions that are causing infertility or not? Is there anything about the mechanism that makes us believe that if we're seizing this subgroup, to say this is the real evidence that

it works? Is there any scientific rationale for that, or are we just lucky that we identified that group and found the biggest difference there?

DR. NOLLER: I saw Dr. Isaacson grab the microphone. Did you?

DR. ISAACSON: Not intentionally, but no, again, I struggle with that, as well. And I don't think that there's any reason that an infertility subgroup would show a greater difference here. At least, I could not come up with one. And again, I didn't see that difference with the modified AFS score versus the original AFS score in that same patient population, though I understand Dr. diZegera's explanation.

DR. EMERSON: Is there a possibility that it could be younger women in that group with less severe adhesions, as compared to those who might be undergoing more other --

DR. NOLLER: Dr. Isaacson, then Dr. Cedars, then Dr. Snyder.

DR. ISAACSON: Probably not, I would say.

DR. CEDARS: The only thing I could say is

possibly what you were getting at in the second part, if the other primary indication was pain, those might be the people with the more dense adhesions, whereas the infertility patients might have the less dense adhesions. I don't know, but otherwise I can't think of sort of a biological plausibility as to why that group would do better. But just more generally in terms of the secondary outcomes, again, there was this debate about whether or not you need to control for the multiplicity in the number of outcomes you have, and I think clearly you do, so I think to say that you wouldn't need to control for that is sort of statistically not valid. So I would think that you would have to do that, which then gets us back to the only one that's significant once you control for that, is the infertility group, which gets back to your question.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: I just wanted to follow-up. All of those endpoints are very, very highly correlated. And the more highly correlated they are, the less adjustment you have to do. Now I don't see a

huge difference. I mean, it's not that looking at all of those make me say oh, now I think it works more than I did before. But on the other hand, I think going to the full fledged adjustment as if they were -- and by the way, it's not independence that Bon Feroni does, it's mutually exclusive that Bon Feroni does -- and so I think that's too much of an adjustment, but I don't know where to draw the line.

DR. NOLLER: Dr. Snyder and then Dr. Hillard.

DR. SNYDER: I was just going to comment for Dr. Emerson. I mean, the AFS score is not used just for infertility patients. It's also used by some people to score patients who aren't desiring fertility, because it's a step at trying to have a reproducible, quantifiable measure, and that's why it was --

DR. NOLLER: Dr. Hillard.

DR. HILLARD: Biologically the things that I could think might potentially be different in this group might relate to the location of the adhesions being too ovarian as opposed to abdominal wall or

elsewhere, or the mechanism of the infertility in the first place being related to PID as opposed to endometriosis. So those are the things that I can think might potentially be different in the infertility group.

DR. NOLLER: Yes.

DR. CHEGINI: In fact, that is really true because if you look at the percentage of patients with reduction, there is no difference much, but then you go to the patient, percent of reduction with patient with primary and some infertility, that's exactly what indicates. And maybe that is pointing out that probably these patients they have more scar on their tubes or uterus, that area on the ovary, versus the other general one that had it much more in the other sites.

DR. NOLLER: So admitting that I didn't do well in anatomy, is the volume, the separation caused by the volume? Will that fit in with that idea that the one liter might cause more separation of those surfaces?

DR. CHEGINI: Most likely, because the

window as you notice under their presentation, they had a three days window for adhesion formation. That is very important in a bone healing situation, but when you get to the scar that are very dense, you never, ever get a dense scar within a week because you need at least three or four weeks before the collagens and material to deposit in order to have a decent amount of material.

With regard to pain, there are also data that actually are showing that there are nerve endings in the adhesions, so when you remove those maybe reduction to pain is that. But, of course, when you fill up the entire cavity and you provide a certain barrier for at least 10 days, or 5 days, or 6 days, of course you reduce that, definitely.

DR. NOLLER: Other comments about the secondary points? Any comment from Nancy, any comment from Division Director or from Staff about the secondary points?

MS. BROGDON: No, no comments. Thank you.

DR. NOLLER: Again, I'm told by the script I'm supposed to summarize. It doesn't sound like

we're very thrilled with the secondary endpoints, that we just kind of -- it's almost sort of, okay. We looked at a lot of things and a couple of them look interesting. It's really we're more interested in the first question and the first analyses. Correct, or am I being too? Okay, moved along well there.

Question three. Question 3 deals with safety, and we have a table on page 3 of our handout that lists the four "serious adverse events." We're supposed to discuss whether we believe that the risk posed by Adept is outweighed by the clinical benefit that's discussed under Questions 1 and 2 that we just finished with. Who would like to talk about safety first? Yes, Dr. Romero.

DR. ROMERO: I guess the main question I had was with regard to what appeared to be a dramatic difference in the rate of vulvar edema in the European experience versus what happened in the clinical trial here.

DR. NOLLER: That difference was interesting to me. The three trials that we have information for, the two small ones and then the

pivotal trial all had 4, 5, 6 percent, but the self-reported large ARIEL trial of vulvar edema wasn't even on the list, but is the explanation, and perhaps we need sponsor -- is the explanation that those serious events were only recorded while the patient was still in the hospital, and vulvar edema might not occur until a day or two later? Why was there no vulvar edema reported in that 2000 or whatever it was patients in the ARIEL database? Can you answer that?

MS. CLISBY: I think in the total ARIEL database, there was a reporting of about .5 percent of vulvar edema, in fact.

DR. NOLLER: There's no reason to believe, though, that it should be different than these other three trials, is there?

MS. CLISBY: Well, I suspect that the difference would be that during a clinical trial, all adverse events are very assiduously reported; whereas, the ARIEL registry wasn't trying to be a clinical trial. It was just an in-use reporting, and those are the numbers that came back.

DR. NOLLER: It was a voluntary reporting,

which is always under-reporting.

DR. ROMERO: But I guess the magnitude of order there is what's striking. I don't know if --

DR. NOLLER: It's a ten-fold difference. Dr. Isaacson.

DR. ISAACSON: I would just say that I've seen quite a few patients with vulvar edema using even when we haven't used large volumes, and it is very self-limiting. It's, I consider, a very minor, minor side effect, and I'm surprised anybody would voluntarily report it because it is just self-limiting. At most, patients may use a little cold compress for up to 24 hours until it resolves.

DR. NOLLER: Back to the general safety, are we convinced that this is a safe product? I see a lot of head shaking. Number four follows from that. Discuss whether the safety data from the ARIEL registry supports the safe uses, Adept as an adhesion prevention solution. We sort of covered that. Yes, Dr. Emerson.

DR. EMERSON: If we distinguish between supports or is consistent with. It's certainly

consistent with, and I just don't know whether -- how trustworthy it is in terms of the voluntary reporting.

DR. NOLLER: Probably not. Yes. Ms. George.

MS. GEORGE: One comment I would like to make so that everybody understands. In Europe, just like here in the United States, they have an MDR reporting-type process, so in the event that there's an injury or a death, or anything like that, they are obligated to report it to their country, and then all of Europe has that visibility, and the manufacturer would be notified.

MS. MURPHY: Nancy, any comments from FDA?

MS. BROGDON: No, thank you.

DR. NOLLER: Let's go to number 5, labeling and training. Does the panel have any comments on the labeling provided by the sponsor? And that was in the materials that we received. And actually, I think, Keith, didn't you say you were going to say something, and then Dr. Snyder.

DR. ISAACSON: I have a couple of comments about the labeling. It's in their first volume.

Section one, draft labeling. Page 7, actually starting on page 8.

DR. NOLLER: Section one?

DR. ISAACSON: Section one. Again, I would like for under number one at the top, it says "a significantly greater percentage of patients, 45 percent versus 35 percent." Again, just because this is labeling and maybe you don't do this in labeling, I'd like to put that as statistically significant greater. That's number one. And number two is, if I just go to the -- at the bottom, there's an A, B, and an asterisk, and to me, the definition of success under A just needs to be clarified, or just written more clearly, some different language. And I haven't come up with that language yet. But again, when I read it several times, it's still not clear to me how they define success.

DR. NOLLER: Good. I think we all struggled with that. Dr. Emerson.

DR. EMERSON: Yes, I think success is a perfectly good word to use in the statistical analysis of the data and things like that, but I think it's a

terrible word to use on the labeling. I think it's better to say that this met the threshold for reduction in lysis rather than putting on the editorial comment that this is a clinical success.

DR. NOLLER: Yes, Dr. Sharp.

DR. SHARP: Just going back to the indications, this is page 3 of Volume One. It says that "it is to be used for reduction of post-surgical adhesions in patients undergoing gynecologic laparoscopic surgery which may include adhesiolysis," so I take it that would mean it would be approved for a patient undergoing a tubal sterilization that had no adhesiolysis. And I just wanted to clarify, so that was not really the group that this was studied in. If we're going to put it in --

DR. NOLLER: Actually, I wanted to raise that, too. The indication is that it -- the way I read this is that it's indicated for those patients where you're going to do -- you're going to remove adhesions, do adhesiolysis, so let's say you're opening somebody with pelvic pain. You don't see any adhesions, but for some reason you take out the right

ovary. To me, this wouldn't be indicated then. Is that right? Or was it intentioned because you thought there were adhesions, since you went in with the idea of doing the adhesions, so the wording here really is hard to understand exactly what was meant.

DR. SHARP: Yes. I think that's the struggle in that we have a group that it was used in clean cases for adhesiolysis, and the other thing I struggle with would be would you use this in a patient in whom you did a hysterectomy, where it's now clean contaminated, and you have exposure to the vaginal cuff, and have this fluid that is now hanging around for four days. That's not been studied, but --

DR. NOLLER: That's so far off this, that would not --

DR. SHARP: But this is saying "undergoing laparoscopic surgery," so really under that definition it could be used if we keep this approach.

DR. NOLLER: Since it may include -- it doesn't have to include.

DR. SHARP: So I think it might be worthwhile to --

DR. NOLLER: Do we feel that it should be more specific for those patients in which you have performed adhesiolysis or for which adhesions are likely to form, or something like that? I mean, I think that's any surgery we ever do.

DR. SHARP: I think adhesiolysis would --

DR. NOLLER: Dr. Miller is really trying.

DR. MILLER: Well, it comes back to one of the secondary points which was even though it was marginal, there was about a 10 percent reduction, or 9 percent reduction in de novo adhesions, so I think many therapies that get approved for a specific indication are going to get expanded by the application, the principle that if a little is good, more is better.

DR. NOLLER: That's true, and that always comes up, and yet we really need to focus on the proposed indication of the sponsor today, but I'm not quite sure what they're asking for based on the way this is written.

DR. MILLER: The narrowest definition would be to just apply the criteria that was used for

entry of these patients in the study.

DR. NOLLER: And that was?

DR. MILLER: For patients undergoing a procedure designed to reduce adhesions.

DR. NOLLER: Let me ask the sponsor, had you intended this to be used just in those patients in whom adhesions are taken down, or had you intended this to be interpreted as a broader indication?

MS. CLISBY: I think in view of the result on de novo adhesions, we intended that it could be used in this broad indication also.

DR. NOLLER: And by broader, you mean any case where adhesions might form?

MS. CLISBY: That's right, so any gynecological surgery laparascopically performed where it was felt adhesions might form.

DR. NOLLER: Dr. Sharp, you raised the issue of hysterectomy. What do you think about that? Are you comfortable with this being done in conjunction with the LAVH where it's an open contaminated --

DR. SHARP: My concern is just the fact

that this stays around for so long. And once you breach the barrier of a clean contaminated wound, we know that the infection rates are higher. We just don't have any data, and it would be great to have that, but I just raise the issue.

DR. NOLLER: Well, we have data from general surgery where they had contaminated wounds, 28 or something percent significant problem. Dr. Snyder and then Dr. Isaacson.

DR. SNYDER: I mean, I happen to like Dr. Miller's suggestion that what we're telling them is in a level of effectiveness, possible effectiveness. But that level is based on the indications that were used in this patient population. I think that practically that's not going to necessarily influence the off-label use if this were approved. But I think if we're doing our job we ought to state what you're saying, what we're specifically comfortable, that there's good scientific evidence for.

DR. ISAACSON: I mean, I would go back to the fact that again we're kind of struggling with the clinical significance, and now if we broaden it to a

whole bunch, might we actually start to do some harm? And that would really be unfortunate, so I would probably like to see it limited to clean cases.

DR. NOLLER: Ms. George.

MS. GEORGE: In the precautions on page 4, the one, two, three, four, five, fifth bullet down they had some precautions, and not being clinical, I'm not sure if that covers it enough based on what you guys are discussing.

DR. NOLLER: Let's take a moment and look at those on page 4.

MS. GEORGE: It's in the precaution section that maybe that would address it sufficiently, or maybe it should be expanded to address that.

DR. SNYDER: It really doesn't, because I think the one you're talking about, it says "in the presence of frank infection in the abdominal pelvic cavity," but it doesn't necessarily talk about a clean contaminated case.

MS. GEORGE: I was referring to the next bullet down, "the safety has not been established."

DR. SNYDER: After unintentional

enterotomy or bowel perforation. And again, the case we're talking about is a clean contaminated case just from opening of the vaginal cuff.

DR. CHEGINI: The other issue is we are talking about adhesion reduction, not prevention. All our discussion has been there, so therefore, when you bring another group of patient that they actually has nothing at all wrong with them, and you put it in there, what are you trying to do, to prevent adhesion? You never establish that those patients are going to form adhesion anyway.

DR. NOLLER: Dr. Weeks.

DR. WEEKS: Basically, in a similar vain, that these patients all, to be included in the study, they had to have adhesiolysis done at least three separate sites, so these aren't all-day every-day laparoscopic patients. And I think it would be over-broad to suggest that this device can be used. And if you just use the term "if adhesion formation is expected," well, that's basically with every surgery you do, so I think we have to say something about the type of patients that were studied, and limiting the

device to similar patients.

DR. NOLLER: Dr. Cedars.

DR. CEDARS: I think one of the problems with restricting it to the type of patients that were studied is they were studied for a specific reason in that you had to lysis a certain number of adhesions so you could then come back at the second look and show that you had a benefit, which is different than saying -- I mean, the entry criteria for the study were more stringent than criteria you might use clinically, which is somewhat different than saying I'd use it for any abdominal surgery, but I don't think you can limit it to just people that would have met the inclusion criteria, because the inclusion criteria were developed based on the fact that they were going to have a second look, and needed something to grade, to stage.

DR. NOLLER: Dr. Miller, then Dr. Emerson.

DR. MILLER: I'm just wondering if we change the labeling the way it's currently written to laparoscopic surgery requiring adhesiolysis, would that not encompass what we're discussing?

DR. NOLLER: Dr. Emerson, Dr. Isaacson, Dr. Snyder.

DR. EMERSON: I was going to second the comment, saying that this patient population was chosen for statistical power rather than for clinical or scientific importance. And recognizing that I'm a statistician, but I'd say that I have sympathy for the idea that it would be prevention of adhesions. Unless there were clinical contraindications to it, I think that it's unlikely that we would ever mount a study to study that separately, and I don't think -- I personally didn't see the safety issue.

DR. NOLLER: Dr. Isaacson, then Snyder.

DR. ISAACSON: Because I think there is another group of patients in whom you expect adhesions to come after you do, say a laparascopical ovarian cystectomy which is clean, but you expect them to have adhesions. You do a laparoscopic subtotal hysterectomy, it's clean, but you know they're going to have some adhesions, and these patients weren't studied here. But again, it gets back to the safety profile where is it safe enough to try it because the

safety profile you assume would be -- I would assume would be the same in those patients that weren't studied. And then we're banking all of this on a very small difference in de novo adhesions.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: Getting back, because I think your fear is the clean contaminated case, because frank infections already rule out its use in somebody you're taking care of laparoscopic TOA on, and it may be better to satisfy Dr. Sharp and I's concern by actually specifically saying that there's no data to establish its safety in a clean contaminated case, because I agree with all the other comments. And we do have the ARIEL results, that if there's any part of the safety that just in the general surgery patients, there was less of a safe cushion there in those patients that had the anasmosis done. And so I really do worry about that clean contaminated case.

DR. MILLER: I guess I still come back to that. I mean, we were struggling a few minutes ago with whether or not this device met the baseline criteria. Now we're talking about expanding the

labeling to prophylactic use, which was never the intention of this study, so it seems like we've gone from being skeptical of the primary endpoints, and now we're on to empowering it to do things that it wasn't studied to do.

DR. NOLLER: Dr. Emerson.

DR. EMERSON: Well, I guess my view is that I'm relatively convinced that it does something about adhesions. I'm just not sure whether that matters, but once we're talking about what the indication is, and doing something to try to minimize the adhesions as we've measured here, I think that it's -- there's pretty good evidence there. Then there's this thing that sort of lurks in the back of my mind of saying well, we often do things in the worst case patients, and then we're really hoping that it will make the bigger difference in the patients who don't yet have any adhesions, and that we prevent them ever from developing; whereas, we don't do as good a job treating that. So I don't see the contradiction in that. I'm still on the fence about whether it matters whether we treat the adhesions or not.

DR. NOLLER: Let me just remind the panel that eventually we will have the chance to consider conditions, one of which could be a change in labeling or different wording at some point, if we feel it's important. Dr. Romero, were you going to say something?

DR. ROMERO: Well, I think I was going to agree with the points that Dr. Miller made concerning the fact that we did put aside for a second this issue around whether the 5 percent threshold was something we needed to consider seriously aside from discussion of the clinical benefit. And the fact that that conversation has now evolved to one where there seems to be -- I know I'm being redundant, but there seems to be a broadening or a less conservative approach, does seem to me to be potentially problematic, and certainly a bit contradictory. And what I was thinking about was to the extent that when it's the appropriate time in the deliberations of this panel to not only consider conditions, but also recommendations around post market activities that the sponsor might undertake, it seems that a recommendation that post

approval data be collected along these lines for potentially coming back to request a broadening of the indication or the labeling, also seems like there might be some scientific credibility for this panel to feel comfortable about if that's an approach that's considered.

DR. NOLLER: Does FDA want to make any comments about our discussion on this point?

MS. BROGDON: Not at this point. We'd appreciate more clarity on this, but later in the discussion.

DR. NOLLER: Other comments?

DR. EMERSON: This is just going back to one comment that on the vaginal bleeding which, by the way, was listed with a P value of .06 using a test that when I'm looking for rare events I don't use. I would use another test where it would have been statistically significant in this trial, but it's just like it's not fair to let them go cherry-picking to make things significant, it's also not fair for me to do that. But this 6 percent versus 2 percent rate, I don't know whether that's biologically plausible that

there would be any activity there, but I certainly think the comment that says "the vaginal bleeding events were not considered to be related to Adept" is inappropriate in the labeling. I work on a lot of clinical trials where people see things that they didn't expect, and invariably they weren't attributed to the treatment, and often we see differential effects.

DR. NOLLER: Yes, Ms. George.

MS. GEORGE: I have a more general question on all of that data that's in the labeling, I guess as a manufacturer, I would not like to have this kind of information put into my labeling because 10 minutes after we start selling devices, this data is now outdated, and I'd secondarily question if any of you would ever read it in the labeling, because it seems like it's smack dab in the middle. It has warnings, contraindications, lots of clinical data that's going to be outdated pretty quickly, and then your directions for use, so it's something that I guess I would like to hear from you guys why you think it's valuable to be in the IFU.

DR. NOLLER: Dr. Sharp.

DR. EMERSON: Just for clarification, what information are you talking about specifically?

MS. GEORGE: From the bottom of page 4 to the top of page 10, because normally you're putting data that is from a study, and then that data could be --

DR. NOLLER: Dr. Snyder has a comment.

DR. SNYDER: I read that all the time, before I use a new product.

MS. GEORGE: But is it normally in the IFU? Because as a manufacturer, I have never, in any of my products, ever in 25 years as manufacturer, nor has the FDA ever asked us to put it in there, so I'm just curious as to if this is common in the IFU?

DR. EMERSON: I've seen it, and not unlike Dr. Snyder, when I'm reading it, I'm reading it for my personal use rather than for a patient, and I'm not sure it counts that a statistician reads such things.

DR. NOLLER: It looks like we have a conference. Dr. Pollard, then Dr. Isaacson.

MR. POLLARD: Thanks, Dr. Noller. I just

wanted to clarify for Elizabeth George, our industry rep, and appreciate the comments, but it's very common for FDA to include this kind of information in medical device labeling, and that's not saying your labeling for your products is out of compliance or anything like that. But this is an implant, and we do have these findings from the clinical trials, and we do -- we are interested in the panel's input on the labeling, and to the degree that you can enrich our appreciation of the findings from the clinical trials as they effect the labeling, but just to sort of set the record, it's very common.

DR. NOLLER: Yes.

DR. CHEGINI: One thing I wondered on table four, I think when we put Adept there and control, control could to somebody who hasn't seen the whole thing, it could be nothing. So, therefore, Lactated Ringers could be practical and mislead in that situation because there's nothing indicating that was Lactated Ringer there.

DR. NOLLER: Good point. Dr. Cedars, then Dr. Snyder.

DR. CEDARS: This is just a small point, because they have a paragraph following table one talking about the labial edema, but it just seemed odd to me when I first was reading through this and they said they were listing events that occurred in more than 5 percent of the patients, but vulvar edema is not in that list, so I wasn't quite sure why. And then I saw it and I kind of wrote why vulvar edema, and then it was in the next paragraph, but it seems like it ought to be in that table, as well, where it's got the comparator of the control group.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: Yes. Actually, I was going to make that exact same comment. And, in fact, I really think it should be moved into the precautions. Dr. Wong in her presentation, she used the term "community practice," is that what it was? I mean, again, if we're talking about your everyday clinician in a small town reading something, they're probably going to read the precautions, at least get that far. And I sure wouldn't want them to think something really unique is going on if the patient on the

morning after surgery has got some vulvar edema. But in the precautions it says pleural effusion, which was -- I mean, I don't even remember that in the adverse events. I think there was one case or whatever, but I think we should at least state there in the precautions that 5 percent of patients -- it is detailed much more in the adverse events, but I just think it needs to be in there for the average practitioner who didn't live in the days of Hyscon to expect.

DR. NOLLER: I'm going to take the Chair's prerogative and ask for a 10-minute recess, and we'll start right where we were, and Dr. Isaacson will be the first one to speak. Ten minutes. Please come back as quickly as possible.

(Whereupon, the proceedings went off the record at 4:28:21 p.m. and went back on the record at 4:40:11 p.m.)

DR. NOLLER: Thank you all for making a 10-minute break possible twice. You will remember that when we broke, we were talking about labeling and training, and Dr. Isaacson was going to make a

comment.

DR. ISAACSON: Just a minor comment, but it's under the labeling under secondary efficacy, and they list that there were 10 variables that were noted, but they only listed the ones that were in favor of Adept. And I just thought in the fairness of being unbiased in the labeling, it would be nice to list the six just briefly that were not -- that showed no difference.

DR. WEEKS: What page is that on?

DR. ISAACSON: That's page 9 at the bottom. It listed the secondary endpoints that were in favor, and didn't list the ones that showed no difference, which I thought it probably should show both since they do that in the other tables.

DR. NOLLER: Any other comments about that? Dr. Snyder, you had another point you wanted to raise.

DR. SNYDER: And I don't want to sound like a broken record, but I asked a number of questions about its use as an irrigant, and I have no concerns about that that changes safety profile or

anything. But nowhere in here do we really have good scientific evidence that it is a superior irrigant, and I have concerns about that, because if you look on page 3, the indications say "Adept should be used both as an intraoperative irrigant and post-operative instillate." And I was trying to toy with how they could be worded. Adept should be used in conjunction with an intraoperative irrigant or as an intraoperative irrigant, and post operative instillate. And I'll tell you my practical concern with this is, is if we don't have any scientific evidence that it is a superior irrigant, because we can only extrapolate that as to the entire outcome measures, that's going to make a huge difference depending on whether you're confining yourself to one liter, or now having to use two separate bags. I mean, that's a practical standpoint.

DR. NOLLER: Dr. Isaacson.

DR. ISAACSON: I agree with you, but the problem is that since we don't have studies where they used it without the Adept as an irrigant, all you can say is it should be used for protocol in which it was

used as an irrigant, as well as an instillate.

DR. NOLLER: Yes, Dr. Chegini.

DR. CHEGINI: The other issue I had was again on page 10, on pain reduction there is, again, no mention that the other groups, they also have pain reduction, as well. So if they were 80 percent reduction in pain in both groups, I think that overall this description has to be written in a much more balanced way, rather than keep giving additional information that Adept is a superior material without giving a good consumer report for people that are using it.

DR. NOLLER: Other comments? Yes, Dr. Cedars, and then Dr. Weeks.

DR. CEDARS: In the directions for use, it talks about after you've completed the surgical procedure and removed all packs and sponges, and while we sometimes, rarely, use packs and sponges in a laparoscopy, that seems to imply a laparotomy, and their indications are for laparoscopic procedures.

DR. NOLLER: Good pick up. I missed that. Dr. Weeks.

DR. WEEKS: This goes back to rare adverse events, and I believe that urinary retention, vulvar edema, vulvar vaginal edema, but severe enough to occasionally require cause urinary retention should be included. That's on page 6, less than 1 percent group.

DR. NOLLER: Thank you. Please, all of you that are bringing these up remember them as we get to a vote later. Other comments? If not, I'd like to go back. FDA asked us to help direct them a little bit more. Let's go back to our bigger problem about use in patients undergoing gynecologic laparoscopic surgery which may include adhesiolysis. How comfortable or not are we with that? That includes any gynecologic laparoscopic surgery. Dr. Sharp.

DR. SHARP: So I guess that would really include I guess tubal sterilization, and just exploratory laparoscopy or diagnostic laparoscopy. And I --

DR. NOLLER: Oophrectomy.

DR. SHARP: I would feel fairly comfortable extending it to surgeries where you're

removing an adnexa. You've got large portions of the peritoneum now exposed. I do think those are the times when you get adhesions, so I don't really have a problem with that. My issue would be do you expose the patient that has no adhesions, you're really not doing anything other than putting a couple of ports in, do you want to expose those patients to potential risk, albeit, clearly this appears to be a relatively safe device.

DR. NOLLER: Such as, like tubal ligation.

DR. SHARP: The tubal ligation and the exploratory laparoscopy. Those would be my --

DR. NOLLER: Diagnostic.

DR. SHARP: Diagnostic.

DR. NOLLER: Dr. Hillard.

DR. HILLARD: I would echo the question. I'm not sure I have an answer, but I'd echo the question because I have patients, in particular adolescents, and I'm understanding that this is not indicated in those under 18, or at least we have no data on those under 18, but take a 19 year old, I'm doing a diagnostic laparoscopy on for pelvic pain.

They may have completely negative findings, or they may have minimal endometriosis, and so the question would be would this labeling include those patients?

DR. NOLLER: Other comments? How do we feel about if the vagina is open, if the bowel is open, if the bladder is open, we all know we occasionally have those problems, would it be indicated then? Adhesions form. Any thoughts? Dr. Sharp.

DR. SHARP: Again, I'll just state, I think I would limit it to the clean cases for the reasons I've mentioned, which would exclude a case when you are breaching the gastrointestinal tract or the vagina.

DR. CHEGINI: It's pretty well established that 90 percent or more patients having any kind of abdominal surgery, they form scars. But fibrinolytics system is very established and developed that they get rid of majority of these scars, the one at least they become relatively filmy or mild adhesion. Those are the one that they are severe, we are the one that we are concerning. So, therefore, anybody having

surgery, largely about 80-90 percent of them, they won't end up having scars at all.

DR. NOLLER: Dr. Weeks.

DR. WEEKS: I guess I would simply say I think the labeling should reflect very closely what has been investigated. And the expansion is going to happen naturally just due to clinician experience and judgment, and I feel a little uncomfortable given that we're struggling with efficacy as it is, putting in the labeling anything that causes a rapid expansion so that this is basically used in almost every GYN laparoscopy patient.

DR. NOLLER: Other comments? If not, we'll move on to Question 6 which deals with post approval studies. And we're asked, does the panel have input regarding any issues that should be addressed in a post approval study? Hearing none -- oh, Dr. Weeks.

DR. WEEKS: I don't know that I feel really strongly about this, but since a lot of the positive data centers around infertility patients, I wonder about gathering data on patients who are

undergoing laparoscopy because of infertility, and looking for future pregnancies. I think it would be interesting, and perhaps really important, therapeutically important to gather data on how successful these patients are later for the subgroup that are getting their surgery because of infertility.

DR. NOLLER: All right. Thank you. Move to the next item in the agenda, which is our second open public hearing. Again, we have not been informed that anyone from the public wishes to speak. If there is someone, would you please rise at this point. Since there are no requests from the public to speak, we'll move to final comments from the FDA and the sponsor. These final comments should not include questions from us or interactions from us. It's just final comments from FDA and sponsor. And by tradition, the FDA will go first.

MS. BROGDON: FDA has no comments.

DR. NOLLER: Thank you. Does the sponsor have any final comments? And we would like to hold these to under 10 minutes, please.

DR. diZEGERA: Thank you, Dr. Noller. We

would -- actually, there will be far less than that, two very brief slides. The sponsor would first like to thank you and your committee for your deliberations. You've considered literally the issues that we have over the years, and we're all kind of in the same place trying to find something to do about reducing adhesions.

These are what we're talking about today, the procedures that are involved with removing them laparascopically, about 400,000 in this country. We have nothing available to us to place laparascopically or approved by FDA for this purpose. The endpoint we're talking about here is adhesions. This is not a surrogate endpoint. This is the endpoint. Previous panels have identified that, Colin Pollard made it very clear that this is the endpoint, not a surrogate endpoint. And the evaluation of our endpoints was done in a blinded fashion, as has been pointed out by both FDA and sponsor. All of the endpoints were determined in a blinded fashion.

A word about the Lactated Ringers solution, that's the elephant in a room, as I said

earlier. Why did we choose that? Previous studies that have come before FDA for PMA review have never used those kinds of controls, if you will. The reason we chose that high volume of Lactated Ringers solution was because we wanted to randomized controlled and blinded study. A lot of biases, the perception of bias exists when those conditions are not met, so we chose Lactated Ringers solution. And the reason the high volume was used is because that in our volume response studies was the volume that was found to be appropriate to achieve the effects for the volumes, for the concentrations. There's no further benefit, so 1,000 milliliters both ways.

And as Dr. Xuefeng Li pointed out earlier this morning, Lactated Ringers actually, along with good surgical technique, actually had a statistically significant reduction in adhesions. So what, in essence, we were competing against, and one consideration was something that had a statistically significant benefit in and of itself, which none of us, as we've all discussed, had ever anticipated. And it turns out we believe very firmly that that's a

volume response effect as we've all discussed. So as a consequence, we're dealing with a very active control.

If I could have the last summation slide, please -- that's not actually what we're talking about in terms of approval. What we're talking about in terms of approval is should Adept be approved in a situation where there is nothing. Prior to this study, patients did not receive 1,000 milliliters of Lactated Ringers solution. They don't today. It's not a standard of practice, and I personally know no one that uses those sorts of post operative instillates.

I think in thinking about Adept then, in and of itself, we can make some fairly straightforward conclusions. There was a consistent clinical benefit in all of the aspects that were presented today. The fertility potential was preserved in the ways that we demonstrated in terms of the low AFS scores, which are adnexal adhesion scores, and in the infertile patients that had high AFS scores we showed that in many of those patients, those AFS scores came down. And, in

fact, three times more than in the active control arm.

We show that efficacy was maintained with increase in adhesion burden, and there was discussion about different types of adhesions, and were filmy adhesions more important than dense adhesions, et cetera, et cetera. I think our position is that all adhesions are important, and as the number of adhesions increase, the clinical consequences of those adhesions become more apparent for the patient, so I think it is important to underline that Adept showed benefit throughout all these groups of adhesions. As they increased, the additional benefit of Adept over LRS was also shown.

Efficacy was maintained with increase in extent of endometriosis. This has never been shown before. Patients with more and more anatomical sites containing endometriosis, we could see ever-increasing benefits. Pelvic pain was also reduced.

We certainly agree with Dr. Cedars comments that a two-month study of pelvic pain following laparoscopy is not meaningful. These are the data that we have, and this is something we'll be

thinking about on a going-forward basis, but the results are what the results are.

In terms of those dense adhesions, I think the fundamental issue with dense adhesions is subsequent surgery from the stand point of view of causing additional problems on an ongoing basis, and as I think we've all shown and agreed to, there's a 50 percent reduction there, which this is the first time that degree of reduction has been shown.

The safety record has been established. Both sponsor and FDA, I think, are in agreement with that. Obviously, this is very easy to use, and that makes it also unique from the standpoint of view of laparoscopic utilization. And I think that becomes very important in terms of the extent of the benefit we can provide patients by having a device that, in fact, is easy to use laparoscopy. There is no alternative. This is an unmet medical need, and I think with the unusually high benefit-to-risk ratio, I think this is an opportunity to move forward in providing this kind of benefit to patients that are receiving laparoscopic surgery. Certainly, we have no

alternatives. Thank you very much.

DR. NOLLER: Thank you. We'll now go to the panel deliberations and vote. Before we do so, Dr. Bailey will read the panel recommendations options for Pre-Market Approval Applications. Dr. Bailey.

DR. BAILEY: "The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, (The Act), as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device Pre-Market Approval Applications (PMAs), that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows. Safety -- there is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use

of the device for its intended uses and conditions of use when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness -- there is reasonable assurance that a device is effective when it can be determined based upon valid scientific evidence, that in a significant portion of the target population the use of the device for its intended uses and conditions of use when accompanied by adequate directions for use and warnings against unsafe use will provide clinically significant results.

Valid scientific evidence -- valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched control, well-documented case histories conducted by qualified experts and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

Your recommendation options for the vote are as follows. Approval; if there are no conditions attached. Approvable with conditions; the panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or further analysis of existing data. Prior to voting, all of the conditions should be discussed by the panel. The third option is not approvable; the panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or that the data do not provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the Chair will ask each panel member to present a brief statement

outlining the reasons for his or her vote." Dr. Noller.

DR. NOLLER: Okay. We'll start with motions. We'll start with the main motion. And again, the three choices are approval, approvable with conditions, or not approvable. Is there a motion for one of these three choices? Dr. Sharp.

DR. SHARP: I move for approval with limitation.

DR. NOLLER: Conditions.

DR. SHARP: Conditions.

DR. NOLLER: Is there a second?

DR. ISAACSON: Second.

DR. NOLLER: It's been moved and seconded that this PMA is approvable with conditions. Now we don't vote on that at this point. What we do now is to entertain motions for the various conditions. Each condition is discussed, voted upon, accepted or not. And when we're all through with the conditions, then we go back and vote on whether or not to accept with those conditions. Everybody understand the procedure?

So I will now entertain a motion for the

first condition of approvability. Dr. Sharp.

DR. SHARP: I move that the first condition be that this be used in clean cases only, and I have a statement here that would essentially change the labeling slightly, if you'd like me to read what I have.

DR. NOLLER: Yes, why don't you read your proposal.

DR. SHARP: So this, I believe, was on page 4, but "Adept Adhesion Reduction Solution is intended for use as an adjunct to good surgical technique for the reduction of post surgical adhesions in patients undergoing gynecologic laparoscopic surgery which excludes breach of the gastrointestinal tract or vaginal mucosa."

DR. NOLLER: Is there a second to that?

DR. SHARTS-HOPKO: Second.

DR. NOLLER: Discussion? Dr. Isaacson.

DR. ISAACSON: I'm wondering -- I was thinking of another way of putting that when it's talking about opening up the indications in that if we could put in the labeling it's indicated for use in

patients undergoing an adhesiolysis procedure. It has not been studied, and the following list of other cases, such as laparoscopic subtotal hysterectomy, cystectomy, what have you, and then a precaution in those that would consider a non-clean procedure. So the point is that it certainly would approve it for all the patients that were included in this study, make note that it was not studied in another set of patients, and then have precautions just as you had listed.

DR. NOLLER: Just the process, we have a motion on the floor that is not that motion.

DR. ISAACSON: I'm sorry.

DR. NOLLER: -- so we'll have to -- but that's good discussion, but we would have to vote on the first. So we're discussing Dr. Sharp's condition as he read it. Dr. Weeks.

DR. WEEKS: May I ask Dr. Sharp again, your statement, what does it say about adhesiolysis again, please? I'm sorry.

DR. SHARP: I don't have adhesiolysis in that. It's limiting it to clean cases or excluding

clean contaminated or contaminated cases.

DR. NOLLER: Yes, Dr. Cedars.

DR. CEDARS: This is just a point of clarification, and it gets back to the difference between the two statements. So the statement as read by Dr. Sharp has an exclusion in the indication. Would that be the way it would be worded, or would you list an indication as a sort of positive statement, and then have precautions or exclusions as a separate -- because it goes to whether or not this motion is accepted, and that's just in terms of how the FDA would list that.

DR. NOLLER: We are providing recommendations for the FDA, so the final judgment will be up to them. But is there any -- do you want to give us any advice here?

MS. BROGDON: We don't generally write indications for use that have exclusions.

DR. NOLLER: Yes.

DR. CEDARS: It would make more sense I think to have an indication for use, and then either have exclusions or precautions as a separate category,

I think.

DR. NOLLER: Dr. Isaacson.

DR. ISAACSON: I know with the labeling for the endometrial ablation devices they have a whole list of circumstances in which the device was not tested, and that was my suggestion for something here, so doesn't mean that it's unindicated or whatever, it just wasn't tested in this particular group.

DR. CEDARS: I guess my concern would be based on the general surgery comments with a much higher incidence of infection, and include, I believe, some deaths from peritonitis, that I think it has been looked at, not in gynecologic surgeries, but in those more dirty-type cases with not an insignificant risk.

DR. ISAACSON: I wouldn't exclude that. I would still include that in the precautions. But this is just to -- instead of opening up to every type of gynecologic procedure, specifically the ones that were listed and the patients that were included, and then list the ones that just weren't studied, so it's not that it was good or bad.

DR. NOLLER: Dr. Sharp.

DR. SHARP: Would it make more sense to, if we don't want to put an exclusion under indication, would it make more sense to put the inclusion or just to state reduction of post surgical adhesions in patients undergoing clean cases of gynecologic surgery. That's saying the same thing in a different way, but you don't have an exclusion criteria.

DR. NOLLER: Dr. Snyder. Were you starting?

MS. BROGDON: I was just going to say, as long as you're stating it in a positive manner, you can do that.

DR. NOLLER: Okay. Dr. Snyder.

DR. SNYDER: I was wondering if we can't use both statements in the precautions, with your specific wording as an exclusion, include a clean contaminated case, and then add the statement this has not been studied, just like you but put that in the precautions.

DR. SHARP: So just to be sure, under the labeling inclusions we would list clean cases, but then under a precautions section --

DR. SNYDER: I was going to say leave the indications as it is. I mean, it says, "For the reduction of post surgical adhesions in patients undergoing gynecologic laparoscopic surgery which may include adhesiolysis."

DR. NOLLER: Dr. Cedars.

DR. CEDARS: Well, if I understood correctly, some of the discussion was that the indication would be for only what had been studied, which was reduction of adhesions following adhesiolysis, and then you could say not studied in terms of prevention of adhesions with myomectomies or whatever other things. But the indication would be only specifically what was studied, which was in the face of adhesiolysis.

DR. NOLLER: That would require a difference in wording. Correct? Dr. Emerson.

DR. SNYDER: So is this question of a possible -- going somewhere between precaution to contraindication, can it be solved somewhat by maybe stronger wording now, but putting also a second condition on some post marketing surveillance of its

use in cases where there has been bowel perforation, or there has been some non-clean surgery, put it on the post marketing surveillance for those events.

DR. SHARP: So you're saying it wouldn't necessarily be contraindicated in a --

DR. SNYDER: Yes. I mean, this is just -- we don't really have any evidence to suggest that we could be so strong as a contraindication. Now if you can state it positively that we say it's a narrow focus, then we still have the thing of putting some post marketing surveillance to be able to assess that. The other way is to say go ahead and allow it with the precaution, but still demand the post marketing surveillance of these situations. I guess I struggle a little bit with the fact that if you're saying we're going to study it in these contaminated cases post marketing, it almost implies that it's okay.

DR. SHARP: No, sometimes it's just a lack of information, that when we don't have that information that you want to register that. We do the same thing in pregnancy with unintended use in pregnancies, you can talk about just watching that, or

you can talk about saying it's contraindicated in pregnancy.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: If you look on page 3, are we comfortable with the contraindication, which is one minor Adept should not be used in patients with a known allergy to starch based polymers or in patients with maltose or isomaltose intolerance.

DR. NOLLER: We have a motion on the floor based on what we heard from FDA. I suspect it would be wise to ask Dr. Sharp if he would consider retracting his motion.

DR. SHARP: Yes.

DR. NOLLER: Would the seconder accept that?

DR. ISAACSON: I accept.

DR. NOLLER: Yes. And then before we can have any more discussion, then we have to have another motion on the floor. Do you have a motion to make?

DR. CEDARS: I do.

DR. NOLLER: Okay.

DR. CEDARS: Can I suggest that we just

take out the statement "surgery which may include," so that it reads "Adept Adhesion Reduction Solution is intended for use as an adjunct to good surgical technique for the reduction of post surgical adhesions in patients undergoing gynecologic laparoscopic adhesiolysis."

DR. NOLLER: Is there a second?

DR. WEEKS: Second.

DR. NOLLER: Discussion.

DR. ISAACSON: Can I -- just a question. So there would be no place where we would say that other surgeries have not been studied?

DR. CEDARS: Well, no. That would be -- I mean, I --

DR. ISAACSON: So that's another motion.

DR. CEDARS: That's separate.

DR. NOLLER: I would suggest we could add another motion for precautions or contraindications if we accept this first.

DR. CEDARS: Well, no. I mean, you had talked about the way it was listed as -- I don't really know that that would be an indication that you

would then say it hadn't been studied in those other groups. But if you're just listing the indication, that's the group in whom or in which, I guess, it was studied, and so we limit the indication to the group in which it was studied. And we might then list -- because the other would be non-evaluated in primary prevention of adhesions.

DR. NOLLER: Go ahead. Did you have something you'd like to say?

PARTICIPANT: No.

DR. NOLLER: Okay. Are we ready to vote on the first condition, which is the change in wording as proposed by Dr. Cedars. There are three choices, you can vote for, against, or abstain. Those voting for, please raise your hand. Those voting against, none. Abstaining -- did you vote for?

(Vote taken -- unanimous.)

DR. ROMERO: I'm not a voting member.

DR. NOLLER: You're not a voting member. It's unanimous, 10-0.

Next condition. Dr. Sharp.

DR. SHARP: Okay. I will change my

condition to list that under the precautions that we state that the use of Adept has not been studied in patients wherein the vaginal mucosa is breached.

DR. NOLLER: Could I ask you to change it to vaginal epithelium?

DR. SHARP: Yes.

DR. CEDARS: Second.

DR. NOLLER: Discussion.

DR. SNYDER: I might suggest that that could just be included at the end of the statement, "The safety of Adept has not been established after unintentional enterotomy, bowel perforation, or opening of vaginal epithelium."

DR. NOLLER: Perfect. Do you accept that amendment to your motion?

DR. SHARP: I would.

DR. NOLLER: Does the seconder agree?

DR. CEDARS: Yes.

DR. NOLLER: Discussion. All those in favor, please raise your hand. It's unanimous.

(Vote taken -- unanimous.)

DR. NOLLER: Next condition. Dr. Snyder.

DR. SNYDER: I'm going to not make a motion. I'm just going to make an observation and see if Dr. Isaacson wants to make a motion.

DR. NOLLER: We can't discuss without a motion.

DR. SNYDER: Okay. I'll make a motion that we also -- if you notice that there's a safety statement that we just tacked on another item to, above that there's a safety and effectiveness statement, and I would like to include in the safety and effectiveness statement that it has not been studied for primary -- what's your word -- primary prevention. And I'm cutting hairs, but one is a safety and effectiveness statement, and the other one we added some real strength to the safety statement by including the vaginal epithelium.

DR. NOLLER: Is there a second?

DR. ISAACSON: I second.

DR. NOLLER: Dr. Isaacson. Discussion? No other discussion? Vote. All in favor. It's unanimous.

(Vote taken -- unanimous.)

DR. NOLLER: Any additional conditions? Dr. Snyder.

DR. SNYDER: Then I would like to amend the precaution section to include the statement regarding labial edema/swelling, as well as urinary retention.

DR. NOLLER: Second? Dr. Cedars seconds. Any discussion? All in favor. Unanimous.

(Vote taken -- unanimous.)

DR. NOLLER: Other conditions of approval? Dr. Isaacson.

DR. ISAACSON: May I ask Dr. Emerson for help on this one.

DR. NOLLER: Please speak into the microphone.

DR. ISAACSON: I would like some help with how we would redefine success or reword that, as you said, differently than how it's listed in the legend on page 8.

DR. NOLLER: Propose a motion, if possible.

DR. EMERSON: I would actually start on

the bottom of page 7, and say that the primary efficacy was defined as the proportion of patients for whom the number of sites with adhesions decreased by at least" -- I'd take out the success rate there.

DR. NOLLER: Decreased by at least three?

DR. EMERSON: Yes. I'd just take out "there was a success rate," and say "first primary efficacy endpoint was defined as the proportion of patients for whom the number of sites with adhesions decreased by at least the larger of three sites, or 30 percent of the number of sites." And then I would continue to just use the phrase about, I guess, decrease in the number of adhesions above the threshold, or above the study-defined threshold. The term "success" is what bothers me.

DR. NOLLER: Is that a motion?

DR. EMERSON: Sure.

DR. SNYDER: Second.

DR. NOLLER: Second by Dr. Snyder. Dr. Cedars.

DR. CEDARS: I guess I was thinking that what bothered you was the -- not the word "success

rate," but the definition that they used. And it was confusing, but I don't think you can change that, because that's the definition that was used for the trial, this decreased by 30 percent or larger of the three sites. You can't -- I mean, it's a confusingly worded definition of success, but I don't know that you can change that because that was the definition used for the trial.

DR. EMERSON: But the word "success" has a different meaning in a statistical study in terms of just defining it for the purpose of the study. We all the time teach in our introductory statistics text when we use the word "success versus failure." But I think reading in a labeling, and particularly when they're calling it a clinical success, when actually this is quite a sub-clinical endpoint that we have here I think is just misleading.

DR. CEDARS: Is that what bothers you?

DR. ISAACSON: Well, yes, that bothered me, but you were right. But the study success, I mean, we have lots of endpoints, and that was just only one endpoint. And that one endpoint is term

under quotations actually on page 8 as success. And I don't know why we determine, or how it's determined that that one endpoint should be called success, when no other endpoint has a name to it. So that, to me, seems misleading.

DR. CEDARS: But that was the primary endpoint or one of the co-primary endpoints. I mean, that was a primary endpoint --

DR. ISAACSON: There are three primary endpoints. Right? On that first one.

DR. CEDARS: Right.

DR. ISAACSON: And this was one, but why was that one called "success," and that's what makes it a little bit misleading in my mind when I try to read through this. I'm just trying to clarify it, actually. As I was reading through this, I found it very difficult.

MS. GEORGE: Wasn't that defined by the first panel that made the decision a couple of years ago, that was their definition that they came out with? I thought that was what these three were, was that was defined by them, so it was -- I didn't think

we had that as a topic to discuss.

DR. ISAACSON: But this is only one.

MS. GEORGE: Right, but I think they defined it.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: If I would suggest an amendment to Dr. Emerson's, because the way he changed things, he eliminated that on page 7, eliminated success rate which -- all right. And then if we just on page 8, and I agree with Dr. Isaacson, it sounds like success may mean more than what it is specifically designed to mean here. There is no reason to even include the stuff in the parens. It would just be pivotal study first primary efficacy endpoint.

DR. EMERSON: And then eliminate A underneath.

DR. SNYDER: Yes.

DR. NOLLER: Dr. Emerson, you made a motion. What do you think of that amendment?

DR. NELSON: I'm fine with that, but I also have to add at the top of page 8 in that

paragraph where it says, "significantly greater percentage of patients." I would just say, "the Adept met this first primary endpoint."

DR. NOLLER: More discussion? I'm going to ask Dr. Emerson eventually to read this back with the changes, but Dr. Isaacson, did you have --

DR. SHARTS-HOPKO: You'd also need to change the axis label on the chart, on the graph.

DR. SNYDER: As well as in the table below.

DR. NOLLER: Were it says "success." Yes.

DR. HILLARD: As far as all the controls that I mentioned earlier, they have to be indicating that they are LRS rather than controls.

DR. NOLLER: Everywhere it says "control" only should say LRS. Do you accept that amendment?

DR. EMERSON: Sure.

DR. NOLLER: We're getting a lot in this. Let's go back over what we propose. Dr. Emerson, can you read, starting on page 7?

DR. EMERSON: On page 7, it would be the first primary efficacy endpoint was defined as "the

proportion of patients for whom," so I deleted the word "success rate which was." The top of page 8, "a significantly greater percentage of patients, 45.4 percent in the Adept group met the first primary endpoint compared to 35 percent." Notice at the top of figure 1, we just have to say "pivotal study first primary efficacy endpoint (percentage of patients)." Similarly, the axis can be "percent of patients meeting first primary efficacy endpoint." Table 3, the title is okay. And then down, "success" is replaced with "first primary efficacy endpoint." And you could say "difference in percent of patients meeting threshold." And under A say, "the first primary efficacy endpoint was met if the number of sites with adhesions decreased."

DR. NOLLER: Does everybody understand that? You essentially eliminated the word "success." Any more discussion? Dr. Miller.

DR. MILLER: Second all those changes.

DR. NOLLER: No more discussion. All in favor of the motion, please raise your hand.

(Vote taken.)

DR. NOLLER: Dr. Miller. Did you vote?

DR. MILLER: Yes.

DR. NOLLER: Oh, I didn't see that. It's unanimous. Are there other conditions? Yes, Dr. Isaacson.

DR. ISAACSON: One simpler one, please. On page 9, the bottom of the page, secondary efficacy, I make a motion that we include the secondary endpoints in which there was no difference shown between Adept and Lactated Ringers Solution.

DR. NOLLER: Second?

DR. WEEKS: Second.

DR. NOLLER: Second by Dr. Weeks. Discussion? No discussion. All in favor of the motion, please raise your hand. Unanimous. Thank you.

(Vote taken -- unanimous.)

DR. NOLLER: Yes, Dr. Cedars.

DR. CEDARS: I have another condition just to remove on that same page, on page 9, under "Directions of Use." It's in italics and "removed all packs and sponges."

DR. SNYDER: Second.

DR. NOLLER: Discussion? All in favor? Thank you, unanimous.

(Vote taken -- unanimous.)

DR. NOLLER: Did you have another condition?

DR. SHARTS-HOPKO: Oh, I do have, but I couldn't find it on page 9. I'm sorry. On page 10 in the section with the secondary efficacy, I think we also wanted to indicate that the pain reduction two months post procedure in the Lactated Ringers Group, I think we also wanted to indicate that pain reduction. "Eighty-three percent of Adept patients," and then we wanted to indicate the Lactated Ringers patients.

DR. NOLLER: That's Adept patients and the LRS. Is there a second?

DR. EMERSON: Second.

DR. WEEKS: Second.

DR. NOLLER: Second, Dr. Weeks. Discussion?

DR. ISAACSON: The only discussion is I think when under secondary endpoints, if we list all

the ones in which there was no difference, that would be included.

DR. SHARTS-HOPKO: Okay. If it's included, okay.

DR. WEEKS: But then perhaps we should eliminate the statement that favors Adept in the text.

DR. NOLLER: Yes. It isn't a bullet item. And before I thought you were adding bullet items, and this is a text item. Is that the point you're making?

DR. WEEKS: Right. I'm just saying that if we're going to leave it to sort of Dr. Isaacson's suggestion that we list all the secondary endpoints for both, the fact that the Adept 83 percent rate appears in the text might lead one to believe that it does better than LRS, so I think we should just eliminate it if we're going to list them both in the table.

DR. SNYDER: Are we in a process of discussion?

DR. NOLLER: We're in discussion, yes.

DR. SNYDER: If we're making a decision

not basing that on secondary efficacy endpoints, I really -- if we were going to take the statistical analysis with the multi-center correction in it, and just list that data, that would eliminate the need to have any bullets added. And then it would only be -- the only thing we'd list is secondary efficacy is that which survived the multi-center test.

DR. NOLLER: More comments? I would like the motion restated, because I'm not quite sure I understand. What did we finally decide?

DR. SHARTS-HOPKO: I was the original mover, and I don't see pain on the pivotal study secondary effectiveness endpoints list.

DR. MILLER: It's the last one.

DR. SHARTS-HOPKO: Oh, sorry. Thank you. Thank you. Anyway --

DR. NOLLER: Your motion is?

DR. SHARTS-HOPKO: We'll print the data --

DR. NOLLER: Please speak into the microphone.

DR. SHARTS-HOPKO: Print the data as reported with the multi-center correction.

DR. NOLLER: Is that your understanding?

DR. EMERSON: Can I suggest that instead they print it without the -- you mean with the multi-center adjustment, or do you mean adjustment for multiple comparisons?

DR. SNYDER: Multi comparisons.

DR. EMERSON: Okay. I would actually just suggest giving it without the multiple comparisons, but explicitly stating that it's unadjusted for multiple comparisons.

DR. SHARTS-HOPKO: Okay.

DR. NOLLER: You want to restate it?

DR. SHARTS-HOPKO: We're going to print the secondary efficacy -- Dr. Emerson, tell me one more time.

DR. EMERSON: I would say that we will provide a table of the secondary efficacy endpoints along with P values comparing the control to treatment arms with an explicit denotation that it's not adjusted for multiple comparisons.

DR. SHARTS-HOPKO: I accept that.

DR. WEEKS: And then I thought we were

going to eliminate the bullets.

DR. EMERSON: That would be replacing those bullets.

DR. ROMERO: Is it helpful just to mention that it's Table 13? Table 13 will be used to replace the narrative.

DR. NOLLER: Does everybody understand the motion? All in favor? It's unanimous.

(Vote taken -- unanimous.)

DR. NOLLER: So far we've been discussing labeling conditions. Let's don't forget the PMA ones also. But, Dr. Emerson.

DR. EMERSON: I just had one more labeling, and that was to remove the phrase about the attribution of the vaginal bleeding events. Just remove that parenthetical phrase.

DR. NOLLER: What page is that on?

DR. EMERSON: That's on page 4 of 10, or page 5. That's been our confusion. There's two ways to refer to every page. So in that paragraph that starts, "In the pivotal study," in the middle there's in parenthesis, "the vaginal bleeding events were not

considered to be related to Adept or control, and none was considered to be severe." I'd just remove that.

DR. NOLLER: Is there a second?

DR. SNYDER: Second.

DR. NOLLER: Second by Dr. Snyder. Discussion? All in favor of that deletion? Dr. Isaacson. All against it? One. Nine to one. You don't have to explain.

DR. ISAACSON: Oh, I thought you said why.

DR. NOLLER: No. Other conditions? Any recommendations for post approval studies? Dr. Miller.

DR. MILLER: One more condition. Didn't we agree that we were going to put the vulvar edema in the adverse?

DR. NOLLER: Yes, we already did that.

DR. MILLER: We did do it?

DR. NOLLER: Yes. That was number three or four, or something.

DR. EMERSON: I will just make this motion, but I'm not wedded to it at all, just so it can be discussed. But the question of post marketing

surveillance for database for infections following accidental bowel perforation or anything like that.

DR. NOLLER: Is there a second? Second by Dr. Sharp. Discussion? Yes, Dr. Isaacson.

DR. ISAACSON: The only discussion is would you limit it to accidental bowel perforations versus intentional bowel anastomosis?

DR. EMERSON: Yes. I mean, I would truly be interested in it, since we don't have any data on whether there's this increased risk of infection, any serious infection would really be what I would be looking at. But there is this idea of do we want to make it outcome-specific? Do we want to make it event-specific?

DR. NOLLER: Dr. Sharp.

DR. SHARP: I like that you left the motion broad, infection. And if it would be possible to dial down, though, to additional detail in terms of the particulars of those case, I suspect that would be possible in terms of whether it was done, in case it was a hysterectomy and someone had used that indication. I think leaving it broad is good.

DR. EMERSON: Yes. I mean, two approaches is one we could say any time somebody knows that they perforated the bowel and they think we'll find out about it whether or not it had infection, or the other is to say any case of peritonitis will gather, and then look to see whether that was associated with a perforated bowel or breaching of a vaginal --

DR. NOLLER: Ms. George.

MS. GEORGE: One question I think about on that is, is that I believe that most of those types of incidents would be captured through the MDR process, so they would already be reportable and tracked by the manufacturer as part of their standard MDR reporting.

DR. SHARP: Part of the MAUDE database?

MS. GEORGE: Yes.

DR. SHARP: Is there a way to make sure that we look at it at one year, rather than just have it be there and never being looked at?

MS. GEORGE: The FDA usually helps us with that, as do doctors who decide to complain back to the FDA.

DR. NOLLER: Dr. Isaacson.

DR. ISAACSON: Question on this that they're asking us to vote on. Are we looking for a voluntary reporting system, or are we looking at something that's mandatory follow-up study?

DR. NOLLER: I would argue that once it's out in the marketplace, everything is voluntary, even if it's supposedly mandatory.

DR. ISAACSON: Well, I mean MAUDE, as you said, is specifically voluntary, so I didn't know if you're looking for a specifically sponsored -- am I wrong on that?

DR. NOLLER: Nancy wants to make a --

MS. BROGDON: The question is whether you would like to suggest that we require some sort of post approval study.

DR. NOLLER: Yes. That's a different -- is that what you had in mind, I think?

DR. EMERSON: I was just suggesting that if this is of major concern, it's something that ought to be looked at, but I don't know right off-hand how you do the study beyond just gathering the data.

DR. NOLLER: The motion was to require

such a study, recommend --

DR. EMERSON: Require the surveillance, but I would probably put it into the requiring.

DR. NOLLER: Okay.

DR. SHARP: Let me just ask the question. Is it different than if we require a study versus just looking at the MAUDE database? Would we get significantly better data with one versus the other?

DR. NOLLER: Nancy, can you address that?

MS. BROGDON: That's pretty much a loaded question, but all devices that are legally on the market are subject to MAUDE and other database data being collected, the MDR reporting system. The specific question is whether you want some additional post market study that has a specifically designed protocol, investigators enrolled and so forth with specific endpoints reported. And those are protocols that we look closely at, and require that the firms do after approval. And they may also include continued observation of patients who were enrolled during the study.

DR. EMERSON: So is there a class of

surgeries that we feel that there will be enough use or close enough to off-label use that we can ask them to specifically look at this? So is there a class of surgeries that you consider safe enough that we can actually ask them just to go ahead and mount a study on perhaps a population it's not really indicated for yet.

DR. SHARP: I guess my concern is by asking them to do a clean contaminated study again, it's kind of saying -- almost approving the use for that, so I'm a little bit torn with that. The other thing is --

DR. NOLLER: You're suggesting that if you accidentally put a hole in something, you don't put the stuff in, so there's nothing to study.

DR. SHARP: Right. And I'm loathe to require a company to do a study that's going to take a lot of time, effort, probably money, if we have comparable data from the MAUDE database. Is that adequate? I'd just like feedback on that.

DR. NOLLER: Anyone want to speak to that?

DR. ROMERO: My assumption would be that

given the first condition that was put on the labeling, that restricts the indication to this particular use, probably will create a motivation in the sponsor to look at whatever data is already required of them to collect to see if it provides the scenario where there is expanded clinical benefit and they might get an expansion in their indication. So my sense is that if data are collected, that there's a built-in incentive to analyze those data.

DR. SHARP: Because we didn't really change the indication in terms of the enterotomy. That's really under a precaution, I believe, rather than the indication.

DR. NOLLER: Right.

DR. SHARP: So indication is still fairly broad.

DR. NOLLER: It's quite broad.

DR. EMERSON: So I would be perfectly willing to withdraw that motion.

DR. NOLLER: Why don't we withdraw it, and then see if anybody else wants to make a similar or does FDA want to -- I see a conference is going on.

MS. BROGDON: Do you need some additional briefing on what the usual post market surveillance for any PMA approved device is? Would that help you?

DR. NOLLER: Can it be done in two minutes?

MS. BROGDON: Yes.

DR. WANG: The major difference between the post market surveillance and post approval studies is post market surveillance is passive, based on voluntary report, and the post approval studies requires clearly identified objective, and the data collection procedures. Does that help?

DR. NOLLER: Does that help? Thank you. Any other conditions? Seeing none. Dr. Snyder. It has to be a motion.

DR. SNYDER: Yes. I'd like to move that we require some sort of post marketing survey study on fertility rates. I mean, we had --

DR. NOLLER: Infertility or fertility?

DR. SNYDER: Fertility rates. Pregnancy rates, excuse me. As amended.

DR. NOLLER: Please state it again. I

don't think everybody heard it.

DR. SNYDER: Just require some data on unassisted pregnancy rates.

DR. NOLLER: Following use.

DR. SNYDER: Following use.

DR. WEEKS: Second.

DR. NOLLER: Second by Dr. Weeks. Discussion?

DR. ROMERO: I guess I would just suggest that it go beyond pregnancy and collect data with regard to births.

DR. NOLLER: Are you asking -- would you like to amend your motion to include data on births, or discussion first?

DR. ISAACSON: I think if you're going to amend it, I would amend it not for births, but to say intrauterine pregnancies, so that way it would eliminate atopic pregnancies, but adhesions -- I don't think there should be any relationship between miscarriages once it's intrauterine pregnancy, so just to document an intrauterine pregnancy rate.

DR. ROMERO: But is the data -- I mean,

it's a longer term follow-up, but clinically it's incredibly significant to the patient, a pregnancy that doesn't result in a birth is not a success, so I don't see why you would stop at pregnancies.

DR. ISAACSON: Intrauterine pregnancy.

DR. ROMERO: Or why you even --

DR. NOLLER: Dr. Weeks.

DR. WEEKS: I would say we might want to know about ectopic pregnancies also, because it may be -- I mean, what we hope to see is that the incidence of ectopics would be lower, and we may, if we just look at intrauterine pregnancies, we may not get that data. I guess I'm the one that originally raised the question about fertility and I was hesitant to bring it up because fertility or successful pregnancies then would depend on more than just what happens with adhesions or tubes, so we may have to ask them to study specifically patients who have preoperative diagnosis of tubal infertility.

DR. NOLLER: One of the problems, of course, is whatever numbers come up with what are they compared to, and that's the trouble with these always,

2 percent, 8 percent, 15 percent. We don't know what it means a lot of times.

DR. SHARP: Would we have a denominator? Is that what you're meaning?

DR. NOLLER: Yes. And compared to national rates of intrauterine pregnancy, ectopic pregnancy.

DR. CHEGINI: Since most of this infertility patient undergo some kind of procedure before having adhesiolysis, so at least you have some kind of establishment to see whether they are related to adhesion, and then following adhesiolysis an application of Adept, that it would help them. If they help them to get at least established pregnancy, at least it would show some efficacy in that point. I probably think extending all the way to the term pregnancy would be wonderful, but I don't think they would be very related because at the moment we have about 30-40 percent success rate in general term anyway with pregnancy going all the way to term.

DR. NOLLER: As you say, we don't have to design the study here, and we shouldn't. If we're

interested in pregnancy rates or live birth rates, we could ask that FDA and sponsor it together and develop a way to track pregnancy outcome we could say in a general way, and they could include whatever is do-able.

DR. MILLER: I was just going to add, though, that I think it is important that we recommend that they monitor both intrauterine pregnancies and ectopics. We wouldn't necessarily suspect this, but we'd hate to believe that a reduction in certain types of adhesions might precipitate the perception of increased fertility that actually result in an increased ectopic rate as a result of the use of this product, so it would be great if it just resulted in an increase in intrauterine pregnancy rate.

DR. NOLLER: Good point. Yes, Nancy.

MS. BROGDON: Dr. Noller, I know that you haven't voted yet on this condition, but Dr. Wang would like to put a question or two on the table for you to discuss. Would that be possible?

DR. NOLLER: Sure.

DR. WANG: Thank you for the panel input,

and one question I'd like to raise is that when we talk about a study on infertility or evaluate ectopic pregnancy, I'd like to have the panel's input also on how we avoid potential confounding factors, because as you all know that pregnancy is affected by many factors, and how can we -- we need input from the panel, and need your expertise on how we conduct or design a study that's feasible. Thank you.

DR. NOLLER: Many confounding factors of pregnancy, particularly in this group. Right? Previous surgeries, previous ectopics. I'm sure FDA can do it. Any suggestions, Dr. Cedars?

DR. CEDARS: Well, I don't have a suggestion other than to say, I mean, I think that's one of the problems with this type of study. And I guess in terms of looking at feasibility for the company to do this, I come back to your question in terms of what's your comparator. And so I guess the question is what would we really want out of this data that we'd be expecting or asking the company to collect, because if it's not done as a study -- I mean, if you're going to say that we approve it and

this agent is efficacious, then you're not then going to do a study comparing using the agent and not using the agent to see if you can improve pregnancy rates. And so, to just look at a study that looks at pregnancy, whether it's tubal pregnancy, or whether it's intrauterine pregnancy, without having a comparator, I don't know what the expectation is. I mean, to look for cases of infection which would be a potential risk of this project and product, and have those reported makes sense to me. But to look at pregnancy as an outcome, if it's not done as a study, which isn't going to happen after this gets approved, I'm just not sure what kind of information you're going to gain.

DR. NOLLER: I could see a report that 18 percent of the women that underwent adhesiolysis and used Adept got pregnant, and 19 percent of those had ectopics. What does it mean? Dr. Isaacson, then Weeks.

DR. ISAACSON: But this came up with the secondary endpoint of having a higher success rate, meaning a lower AFS score than the patients who

specifically had a chief complaint of infertility, and so I agree with you. I don't know how to make it a useful study, but then if you don't make a useful study, then it's hard to emphasize that particular subset of patients who are infertility patients.

DR. CEDARS: But that's the whole point, is I'm not sure that you can emphasize that group, because you can't ever prove the point. I mean, the study is not going to happen, and so I don't think it's reasonable to expect of the sponsor that they do something that isn't going to happen.

DR. NOLLER: Dr. Weeks.

DR. WEEKS: That's definitely why I hesitated to propose it, but I think what we'd be looking to do is use historical controls in tubal patients whose infertility is a tubal factor in fertility only, and the historical control data is fraught with problems, too, but if you see a fertility rate that's 100 percent higher than what you're seeing in your historical controls, then perhaps there's something there. And, otherwise, you just have to sort of walk away.

As far as burden on the sponsor, they're going to be following these patients anyway, so that if you just made an observation period of say a year or two, it wouldn't be that big a burden.

DR. CEDARS: Well, I would make two comments. One, I don't think you can use historical controls because we don't operate on people with tubal disease any more, because IVF has such high success rate, so the people who would be operated on with a diagnosis of infertility are going to have way more mild disease than what the historical controls were when we operated on everybody because there wasn't an alternative, so I don't think you can use historical controls. And then secondly, I don't think that your comment that they're going to be following these people anyway - we have no evidence that they're going to follow these people. They have no incentive to follow these people once this gets approved, so I don't think they're going to be following these people other than if events are reported. But as a routine, to follow all the people in whom this device is used, it's just not going to happen.

DR. ISAACSON: Right. I'm sorry, I didn't mean the sponsor, just the clinicians. Your point is taken.

DR. CHEGINI: I think that is probably exactly what you said, because we have kind of concern about general success of this material. But we are trying to beat it up to the points, putting a lot of condition in order to make ourselves satisfied with our general concept. I think really you have to figure out that the sponsor is not going to do a lot of these, even if you put conditions, because they are not possible to do.

DR. EMERSON: I think we have to come down with that if we vote this as being approvable with our conditions, we're voting on the fact that an indication of decreasing the rate of adhesions at whatever level is what we're saying is okay, and then that's just it.

DR. SNYDER: I withdraw my motion.

DR. NOLLER: Do we want to make another stab at it? Any other conditions?

DR. HILLARD: Can I just raise an issue.

DR. NOLLER: We can't hear you. Please speak up.

DR. HILLARD: I'm presenting this more for discussion, but the clinical question that I would like to see is whether or not this really would be helpful for the primary prevention of adhesions, and so the motion would be that this product be studied in a group for the primary prevention of adhesions.

DR. NOLLER: Is there a second?

DR. EMERSON: I would second that.

DR. NOLLER: May I ask FDA, is that another PMA?

MS. BROGDON: I think it is, because that is a population not included in this indication for use, so it would be another study.

DR. NOLLER: Okay.

MS. BROGDON: Probably a PMA supplement.

DR. EMERSON: And I just might add that it would be very hard to do to define the group that you're sure don't have any adhesions a priori.

DR. HILLARD: So it would be scope and find a negative scope.

DR. EMERSON: Right. So that would be that you have to basically randomize an awful lot of people.

DR. HILLARD: Do a second look.

DR. ISAACSON: No, I disagree with you because you know, again, if you did those or you're doing an ovarian cystectomy, you're doing a laparoscopic subtotal -- most of them don't start with adhesions, and they're be fairly easily randomized.

DR. EMERSON: That would be a study for a new indication, and I don't believe you can make a manufacturer to ask for a new indication. Am I correct?

DR. CEDARS: Well, it's only a new indication because we took out -- we changed the indication that said laparoscopy that included adhesiolysis. It was my understanding that the intent initially was to include that group.

DR. NOLLER: Point well made.

DR. SHARP: I think the original indication as it says here, it says "gynecologic laparoscopic surgery which may include," so it was

very broad.

DR. NOLLER: Discussion? Ready to vote on that condition?

DR. CEDARS: Was there a second?

DR. NOLLER: Yes, Dr. Isaacson.

DR. CEDARS: But can we vote, I mean, can we -- I thought that we couldn't do that because it was a second indication. I mean, can we even vote that as a condition?

DR. NOLLER: I think we have wide latitude on what we can suggest, but FDA doesn't necessarily have to do anything that we suggest. Nancy, will this give you problems?

MS. BROGDON: Yes.

DR. NOLLER: Yes.

MS. BROGDON: First of all, this hinges on whether you're successful in voting for a new indication for use. If you are, then this would be a separate indication for use, and it shouldn't be part of your conditions of approval, because it would be by definition a different study, a different indication for use. So maybe there's some --

DR. NOLLER: It's not appropriate to this.

MS. BROGDON: Right. Maybe there's some way you can work this into your contingencies, but it escapes me right now how you would do that. I guess you would have to wait to see what happens with your main motion, and whether all these conditions hold or not.

DR. NOLLER: Assuming they do and we vote to approve with the conditions we've already approved, we don't have any other choices, though, after that. We're finished, aren't we? Yes. Okay. Somebody, unless we start over again. Now we have a motion on the floor, we need to vote it up or down.

DR. CEDARS: But I guess I feel like we can't really vote it up or down because it's not valid. It can't be part of a condition for the indication we have already selected, so they're mutually exclusive. So I don't think we can vote it up or down.

DR. ISAACSON: We can withdraw it.

DR. CEDARS: We can withdraw it, but I don't think we can vote it up or down.

DR. NOLLER: I'm being directed that we can't vote on this.

DR. HILLARD: It's withdrawn.

DR. NOLLER: Thank you. Any other conditions? Hearing none, it's been moved and seconded that Innovata's Pre-Market Approval Application number P050011 for the Adept Adhesion Reduction Solution be conditionally approved with the nine conditions of approval the panel has just voted in favor of. All in favor of the main motion with the nine conditions of approval that passed, please raise your hand. I note for the record that it's unanimous, all panel members voted for it.

(Vote taken -- unanimous.)

DR. NOLLER: Is the recommendation of the panel to the FDA that Innovata's Pre-Market Approval Application number P050011 for the Adept Adhesion Reduction Solution be conditionally approved with the previously voted upon and passed conditions? I'm now going to ask each panel member the reason for his or her vote, starting with Dr. Cedars.

DR. CEDARS: I support approval with the

conditions based on the fact that there is no currently available system to prevent post operative adhesion reformation during laparoscopy, and the data supports beneficial efficacy, and safety data is reassuring.

DR. NOLLER: Dr. Sharp.

DR. SHARP: I vote approval based on the data that was suggested. This is a safe device, and that two of the three co-primary endpoints were satisfactory, to my satisfaction.

DR. NOLLER: Dr. Hillard.

DR. HILLARD: I voted as I did on the basis of clear safety and the basis of statistical significance of the endpoints and probable clinical significance.

DR. NOLLER: Dr. Chegini.

DR. CHEGINI: I have considerable reservation for the efficacy comparing to Ringers Lactate, but as an investigator in the field and recognizing that this material is comparatively helping some of the patients during her first period of the clinical treatments, I voted for that.

DR. NOLLER: Dr. Weeks.

DR. WEEKS: I think the safety data is convincing. I am not as convinced about efficacy, and would have not supported the device if we didn't get in, or at least try to limit the indication to adhesiolysis. I have some real concerns about efficacy, but I do maternal fetal medicine, and relied on the input of the folks that do GYN surgery, and their discussion swayed me to vote for it.

DR. NOLLER: Dr. Sharts-Hopko.

DR. SHARTS-HOPKO: I was here for the discussion 2001, and so it's been interesting to see the careful and collaborative work of the company and FDA in coming to this point. Safety data also for me is compelling. I think that this product offers an important addition to the health and safety of the care of women. I anticipate with eagerness the flood of competition that will soon emerge.

DR. NOLLER: Dr. Snyder.

DR. SNYDER: I mean, again, with the safety profile and the experience, and the data that we've got not only with this agent, but with years of

the Extraneal, I considered that not an issue. I'm not as concerned. I do think that we not just have some scientific evidence, but we've got a randomized control trial that showed some efficacy in decreasing adhesions. And I don't think I'll still be practicing when we can answer the question whether adhesions cause pain or what other problems that they cause, but I mean, this is a randomized controlled trial, and I feel like in the end when I make a decision like this, would I want myself to have this available, or one of my family members have this available, I think I clearly would want them to have this available.

DR. NOLLER: Dr. Emerson.

DR. EMERSON: I think the results of the clinical trial show that there is activity with regard to reduction of adhesions. I don't think it's absolutely clear whether that translates into clinical effectiveness on endpoints, although I also do believe that there's enough uncertainty as to the activity of the control that it may well pan out, and given the lack of a safety concern, I felt that the adhesiolysis reduction in adhesions was sufficient to warrant its

approval.

DR. NOLLER: Dr. Isaacson.

DR. ISAACSON: I second everyone else's thoughts, and that I was compelled, certainly had a low threshold for approval based upon the safety data. I do believe that there's no way for us to determine based on this study whether there's clinical benefit at this point. I was compelled to vote for it because of Point Two, in which it showed a clear benefit as using Adept as its own internal control, and I think there's going to be quite a bit of discussion hopefully when this gets to market regarding its comparative benefit versus Lactated Ringers Solution.

DR. NOLLER: Dr. Miller.

DR. MILLER: I think I will always have trouble thinking of this product as a device, but that notwithstanding, I compliment or I echo everybody else's sentiments. I think that there is clear efficacy. There seems to really be no major safety concern, and it's in a niche market without competitors, and has potential for the benefit of women.

DR. NOLLER: Comments from our consumer representative, Dr. Romero.

DR. ROMERO: Yes. I think that from the perspective of the public health community base consumer perspective that it's reassuring, the safety profile from the studies done is reassuring. I am concerned, and I don't think there's any way of knowing that at this point, but I'm concerned when the product does come to market what the experience of consumers will be with regard to the information that they're given preoperatively. And what I mean about in terms of that specifically is that there be responsible conduct on the part of the information provided by the manufacturer, as well as clinicians, in terms of what patient's expectations should be. I think that's where oftentimes very good and useful products in particular contexts may be built up among consumers in terms of their expectations, and where problems ultimately arise that need not, so I guess that's just my concern just down the road.

DR. NOLLER: Thank you. Industry representative, Ms. George.

MS. GEORGE: I, too, had lots of trouble dealing with this being a device, as an electrical, mechanical, and biomedical engineer it didn't seem like a device to me, but I guess it is. I concur with everything that everybody has said today, and I was happy that the conditions did not include a post market study, because I think all of you did a great job of bantering that around, trying to figure out even how to do one, so I was glad that this will allow them, the sponsor, to get the product to market pretty quickly. And I think they're probably incented, as a couple of people mentioned, to start doing some of those future studies and monitoring it very closely to expand their indications for use. So that's it.

DR. NOLLER: Final words from FDA, Nancy?

MS. BROGDON: I just want to thank the panel for your preparation time, your travel time, your expertise, and your thoughtful discussions on this device.

DR. NOLLER: Three little bits of housekeeping. The books dealing with this device should be left on the table. They will be picked up

by FDA and shredded. Please, please do not leave the material for tomorrow on the desk, though, or it will be shredded and it'll be gone.

The following persons need to meet with Dr. Bailey up here, right here, immediately after the meeting. Mr. Pollard and Mr. Kuchinski should also be here, but Dr. Snyder, Sharp, Emerson, Cedars and Isaacson need to see Dr. Bailey right after this meeting. We will meet again at 8 a.m. tomorrow morning in this room. This meeting of Obstetrics and Gynecology Devices Panel is now adjourned.

(Whereupon, the proceedings went off the record at 6:07:33 p.m.)