I would like to note that FDA's review of this device is ongoing.

In my presentation, I will cover the history of the PMA, the indications for use. I will describe the device, and I will provide an overview of the pre-clinical review. This information is important to you because it provides a background on the device you will discuss today.

This slide gives you an idea of the history of the FDA's review. On January 8th, we received the PMA. FDA sent a letter of questions to the Sponsor on April 15th, and the Sponsor responded to the last of these questions on September 10th. As you know, we are here today, December 11th, to get your input regarding this submission.

The FC2 female condom is indicated to help prevent HIV/AIDS, other sexually transmitted infections, and unintended pregnancy. This statement is the same as that for FC1.

I will now describe the device. As you can see, the FC2 female condom is comprised of the outer ring, sheath, and inner ring. The inner ring is polyurethane. It's the same as that for FC1, and it aids in insertion. Both the sheath and outer ring are made of nitrile, and the sheath is made via a

dipping process similar to that of medical examination gloves, as you've also heard from the Sponsor. It does not have a seam, like FC1. The outer ring is made by rolling the open end of the condom sheath.

This table shows the dimensions of FC1 and FC2. Relative to FC1, FC2 has a thicker sheath and outer ring but otherwise similar physical dimensions.

In general, nitrile has lower tensile properties and lower tear resistance compared to polyurethane. However, FC1 has a seam, and the tensile properties of FC1 as measured across the seam, that is, the weakest point, were equivalent to or better than the bulk tensile properties of FC2. In addition, the Sponsor mitigated differences in the material properties by increasing the thickness of FC2.

And the results for air-burst testing are comparable, although the specifications are different. This means that when the condoms are filled with air, FC1 and FC2 can hold about as much air pressure and volume before they burst.

Since FC1 approval, the Sponsor made changes to the way they make the device, and just a reminder, as you know, the FC1 is the control condom

for the RHRU study, the clinical study for this PMA. FHC compared data from FC1s produced at about the same time as the pivotal clinical trial for the FC1 PMA, that is, around 1989 to 1990, to data from FC1 from the same lot used in the RHRU study. The data show that the FC1's use in the RHRU study had as good as or better properties when compared to the original devices.

Additionally, FDA reviewed biocompatibility, thermal properties, viral penetration, bioburden testing, and a three-year shelf life justification for FC2 and found this information to be acceptable. We are currently reviewing FC2 compatibility with a variety of commonly used personal lubricants.

Based upon this information, it is clear that FC2 is different from FC1. The outer ring and sheath are made from a different material, and although the nitrile material has lower physical properties, FC2 is thicker and has no seam. However, it is difficult to predict in-use performance based solely on physical properties. This underscores the importance of an acceptable clinical study, so please consider this when determining if the information from the RHRU is adequate.

Thank you. I would now like to introduce Dr. Julia Corrado who will discuss the clinical study in more detail.

DR. CAREY-CORRADO: Thanks, Elaine. Good afternoon, everybody. I'm going to try to cover very briefly historical perspective on female condoms. I'm going to talk about the PMA that's the subject of our meeting. And then, finally, and summarize our clinical review issues. And to some extent, I feel that our presentation has already been made and the counterarguments have already been made. But, nevertheless, I'm going to go through what we had planned to say.

I think it's interesting to note that the concept of a female condom has been around even before the 20th century. I found an interesting reference in a classic book on contraception that was published in 1938 by Norman Himes that described a female condom that was used in northern South America apparently during the 19th century. And it was described as "a pod similar to our milkweed pod, which was cleaned out, one end snipped off, and the closed end inserted into the vagina."

In the 20th century, Colin Pollard also noted that there was a female condom that was

actually in commercial distribution in the United States. It was the Gee Bee Ring, probably named after Gene Beadle, who was a pharmacist who invented it. And I'm going to read from the instructions for use that accompanied that device just very briefly.

> "The Gee Bee Ring method consists of a large sac of prepared animal tissue which is properly fitted in a plicated ring and tested by filling with water.... It is inserted into the vagina by the female with the aid of a test tube, when properly lubricated."

So it was 50 years or so after the Gee Bee Ring had been introduced that FDA received a submission for the FC1 female condom.

The reason we're here today, of course, is to talk about the PMA for the FC2, and there are some unique aspects to this PMA that led us to think that we had review questions we wanted to pose to the Panel, the first of which is that the pivotal clinical trial for the FC2 did not evaluate contraceptive effectiveness or STI risk reduction, both of which are identified in the indication for use of this device.

Also, the clinical data were entirely

obtained outside of the U.S. This isn't truly unique. However, it's relatively rare that all of the clinical data are outside U.S. data.

And, finally, we felt that the public health impact of the FC2 was certainly in the near-term more likely to be felt outside of the U.S., although I have to recognize that we had some very impressive speakers today who have described how such a device might offer benefit to women in the U.S. as well.

The data on contraceptive effectiveness and STI risk reduction are being inferred from a pivotal clinical trial of the Reality Female Condom. That was the first version of the female condom and developed by the Female Health Company. The PMA for the FC1 was approved in May of 1993, and even at that time, there were two Panel meetings, and during the Panel meetings, testimony was given by the public regarding the urgent need for female initiated prophylaxis in the AIDS epidemic. So we're having -- you know, we're -- today's events are mirroring to some extent what happened at that time.

I'm going to summarize that pivotal clinical trial of contraceptive effectiveness of the FC1 because, again, the contraceptive effectiveness

data from that study ultimately would go into labeling for this new device if -- depending on how things work out today.

This was a six-month contraceptive effectiveness study. It was conducted at six sites in the U.S. There were three outside U.S. sites. However, it was felt that the data from the U.S. and non-U.S. sites were not poolable and, therefore, I'm only going to be talking about the U.S. data.

Of 221 subjects enrolled in the U.S., 147 completed the study. Of the women who were lost to follow-up or who discontinued, one of the reasons was accidental pregnancy. And that's what I've highlighted on this slide so that you can see that of the -- of 221 women, 22 became pregnant unintentionally during the course of the study.

The conclusion of the study regarding pregnancy rates at six months are as follows. As seen from this slide, the six-month gross cumulative pregnancy rate was 12.4, and the six-month gross cumulative life table pregnancy rate during perfect use was 2.6.

The six-month data were projected to 12 months. The data that are presented in the labeling for the FC1 are 12-month data, and you can see that

for typical use, the rate was 21 percent, perfect use, 5 percent, and the labeling does include a table that compares -- that gives the user the possibility of comparing those rates against male latex condom rates as of the time of approval of that PMA.

So this slide needs to be updated. Dr. Leeper told us this morning that the number 125 is no longer current. It's actually over 165 million Female Condom 1 devices have been distributed worldwide. However, the percentage of women in the U.S. who are relying on the FC1 is small compared to outside of the U.S.

We've heard that there were important reasons for developing the new device, in particular, to lower costs and make the device more accessible while maintaining design. The FC2 pivotal clinical trial was conducted at the Reproductive Health and HIV Research Unit, the RHRU, which is how we're going to be referring to this study, in South Africa. And it was conducted between January and September of '04. This clinical trial was not submitted to FDA as part of the pre-IDE process whereby FDA gets a chance to look at clinical trial designs before the study starts and offer suggestions. That did not happen in this case. Excuse me.

So I'm going to now present our review of the study. Again, you've had a very good preview of some our review issues, but I'm going to divide my review into sort of two sections, the first being just going over design, study objectives, primary endpoints and research question. And then I'm going to direct -- excuse me -- I beg your pardon -- the Panel to Discussion Question 1, which really is not data-driven from the standpoint of study outcomes. It's more of a global question asking the Panel to talk about does the study design and endpoints have the potential to support the new PMA.

After we go over the design issues, then we're going to talk about some of the study data, including the demographics, how it was executed, the study results, and in issues related to study methods for data collection.

Dr. Beksinska has already gone over much of this -- thank you very much. Thank you.

Dr. Beksinska has already talked about the study design, and it was her study, so I'm just going to very briefly say it was prospective, randomized. We have double-blinded in quotes because of the impossibility of truly blinding the subjects and the staff because of the seam that is present on the FC1.

And the Sponsor has acknowledged that.

This was a multi-center crossover study comparing FC1 and FC2. Objectives were to compare the rates of clinical and non-clinical breakage, outer ring displacement, which we're going to call invagination, misdirection of the penis, and slippage, and adverse events. And there was a secondary objective, which was to compare acceptability. I am not going to be talking about those outcomes. The primary endpoint was the acute failure rate of the FC2 versus the FC1. Again, these are breakage, slippage, that is, coming out of the vagina, invagination, and misdirection of the penis alongside the condom.

The research question, as FDA understands it, was as follows. There was an assumption that the breakage rate for FC1 would be less than 5 percent. And the test was if the breakage rate for FC2 exceeds that standard, that is, is greater than 5 percent, the new condom will not be considered for further development and testing.

So, at this point, I'm just going to note -- I'm not asking for a discussion now -- that the first question the Panel is going to be talking about, basically, is the adequacy of the study design

to support gathering data that would constitute valid scientific evidence to make a finding of reasonable assurance of safety and effectiveness. Long-winded, but that's sort of -- and that, I would have to say, is probably at least as important, if not the most important, question that we have for the Panel today.

So in terms of inclusion/exclusion criteria, many of these seem intuitive. I do want to point out that everyone had to be using a hormonal contraceptive, IUD or tubal ligation, as has already been mentioned. The exclusion criteria were known or suspected active STI or allergy or six weeks post-partum. The study population included five groups of patients at three sites in South Africa.

And in terms of how the study was conducted, prior to the condom use, the study nurse briefed the subject on her responsibilities and the study procedures. Verbal instructions were given for inserting and removing the condoms, and education was given regarding the need to use it correctly. Subjects had to be responsible for accepting random assignment to the sequence of use of FC1 or FC2. They were advised to use ten of each type of condom with their partner within the two to three-month study period. So ten condoms over approximately

eight to twelve weeks. They were told they needed to complete the coital log for each use and to return for follow-up after ten uses of each condom.

At the follow-up visit, as we have already heard, an interview took place in which the study staff asked each subject questions that were included on a 56-question questionnaire, and the questionnaire covered the following subjects: the number of condoms used, regular or casual partner, functional performance of the condom during use, adverse events, and acceptability criteria. Also with the follow-up visits, a vulva inspection was conducted.

So, in terms of the demographics, again, there were five groups: students, urban family planning, rural family planning subjects, STI clinic subjects, and commercial sex workers. The total enrolled was 276. We can see the mean age in each group, ranging from 23 among the students to 35 among the STI clinic patients.

We collected data from the PMA regarding the percentage who had a regular partner. Sometimes whether or not a person has a regular partner may influence the -- their scrupulosity in terms of using the barrier method. We also include mean education level and whether the subjects were engaged in

employment.

This table gives you a breakout in terms of contraceptive use at the time of enrollment in the study. I just want to make two points with this slide. That is, that if you look at the far right-hand column, the most common form of contraception was injectable followed by male condom, and the bottom row tells you how many subjects in each group were using female condoms as part of their birth control and prophylaxis. It didn't mean that they were relying exclusively on it, but they -- in other words, they had experience with female condoms.

So of the 276 who were enrolled, 233 presented for the first follow-up visit, and 201 completed the second follow-up visit.

And this slide shows you more or less the accountability, who in which group showed up for each of the follow-up visits. The commercial sex workers actually had very good follow-up. At the first follow-up visit, the rural family planning subjects also had very good numbers.

So Dr. D'Agostino raised a very interesting question this morning, and it had to do with failures per condom use and whether we were looking at the right denominator. And so this table presents

failures based on total number of condoms used. And I guess I'll start by saying the very bottom row shows the total number of failures for the acute failure modes. And it's actually sort of a subset because, for example, invagination was -- there were many more -- there were many partial invaginations, shall I say. However, there were only ten complete invaginations in the FC1 group and 17 in the FC2 group. And I'm just making this point to explain why the numbers you see here might not line up exactly with the number of total failures the Sponsor mentioned this morning, which was I think 184 or 186.

So if we look at the total failures, the rate of total failures of all types when you combine them is 2.4 percent for FC1 and 2.07 percent for FC2. I'm just giving you the point estimates. Dr. Zhang, our statistician, is going to give you a statistical review of these numbers. So that if that's that total percent of failures, for each failure, it's well under 2 percent.

And that is going to lead me to my next slide, which is a table you have in your Panel pack. It's a table that Colin Pollard showed you already today. And the point here is that in the last column, you can see that if you add up -- from a

number of studies that are represented here, if you add all the percentages of failures for the four failure modes, you get total failure rates that range from 5.6 to 11 -- no, actually to 19.5 percent. And, yet, we see that the total combined failure rates in our study are much lower than that.

And so we're just trying to illustrate that there is some uniformity, as Colin said, among reports of breakage but, obviously, there is -- the reporting slippage, misdirection, invagination is more of a gray area, and, obviously, there are issues in terms of collecting data on those outcomes.

So to get to, to at least attempt to get to Dr. D'Agostino's issue that he raised this morning, if we look at acute failures per subject, the percentages for each of the failure modes goes up obviously because the denominators are so much smaller here than the total number of condoms used. On this slide, it looks like the rate of acute failure per subject is highest for penile misdirection.

I highlighted invagination, though, because I want to talk a little bit more about that. And the reason is that there were many partial invaginations that occurred. And we're going to look at the

failure rates for partial invagination, also called outer ring displacement.

So, you know, I'm going to skip this slide because this is not -- this doesn't logically follow. Here is where I want to go with this discussion. If you look at a per-subject, acute failure, invagination on a per-subject basis, and if you combine complete and partial displacement, what we see here is that the rate of subjects who experienced either on, complete or partial on displacement is relatively high, 23 percent for the FC1, you know, comparable, almost 19 percent for the FC2. And so at a per-subject level, there seems to be, of all the failure modes, something going on here with invagination.

The Sponsor recognized this in the PMA. And they felt that it was possibly related to a problem with inserting the condom too far into the vagina such that -- and also asymmetrically such that the penis may push the outer ring into the vagina. And so the Sponsor has recommended that if this device is approved, that the instructions on proper placement should include that the outer ring be held by the woman during insertion and that the couple be aware of the outer ring during sex to ensure that it

does not get pushed inside the vagina.

So our review wouldn't be complete without mentioning safety. From the RHRU study, the following safety outcomes were reported. The most common adverse event was discomfort during insertion, which was very comparable across the two groups. But on a per-subject basis, it was relatively impressive at almost 14 -- 13 to 14 percent of the subjects reported discomfort during insertion.

The next most common, although it is not in the order on the slide, is the fourth from the bottom, uncomfortable to use, 5 percent for the FC1, 2.3 percent for FC2. We did not do a statistical analysis. I do not know whether those would reach statistical significance in favor of the FC2. But, nevertheless, it gives you the idea that overall the adverse events were not serious adverse events, and they, in general, are related to discomfort.

So, at this point, I want to talk about FDA's review regarding methods for data collection in this study because, as we've seen, the outcomes are certainly comparable across the two arms of the study.

You've already heard about our concerns with the coital log. The coital log was intended all

along to complement the study questionnaire. It was not intended to be the primary -- to constitute the primary database for the study, and it was intended for the subjects to be able to refer to it during the follow-up visit. So we have identified limitations in the coital log, and you have heard them. I'm not going to spend much time.

The coital log represented five weeks, the data for which period of time was to be entered on a single page. There was no entry for slippage per se. It was not designed to record the number of failures on days when more than one female condom was used, and, obviously, the Panel is very much on to that and have already asked numerous questions in that regard.

Thirty-eight percent of the coital logs were missing at the follow-up visits. So whereas the subject was not lost to follow-up, 38 percent did not have coital logs when they returned. And the most important fraction of those who were missing coital logs was the commercial sex workers, of whom I believe there were 59, and none of whom came to a follow-up visit with a coital log.

This is just a snapshot of the coital log. This was only two weeks. It actually went out five weeks, and I'm not going to spend any more time on

that because the points regarding our concerns related to this have already been expressed.

In terms of the subjects who completed follow-up visits and who had coital logs, except for the commercial sex workers, those with coital logs, the rate of showing up with a coital was anywhere between 70 and approximately 90 percent.

Now I'm going to talk about the study questionnaire, which was completed during the follow-up interview. There was a time lag obviously between the condom use and the interview. The questionnaire had 56 questions on it covering sociodemographic issues, experience with the female condom, comfort, removal, stability, and acceptability. And the numbers in parentheses are the number of questions that related to that general topic.

Dr. Beksinska has already told us that two questions on this study questionnaire were designed in general to elicit any type of failure mode information, a subset of which would have been slippage, and so that although the coital log did not include slippage for the reasons that she mentioned, nevertheless, there was an opportunity to elicit information on that acute failure mode by asking these questions in the questionnaire.

So as I wind down, we noted that there are potential problems with data collection, including the missing coital logs, the issue of days when more than one condom was used, the issue of not having an entry for slippage, and the fact that it was a single page.

In terms of where does that go, I mean, we can't quantify -- actually, we can't quantify whether these have an impact and, if they do, to what extent. However, in general, we do feel it's fair to say that there's a potential for underreporting of failure modes based on the outcomes from the study. One reason is, of course, loss to follow-up. We're concerned that if you base your data on face-to-face interviews, there might be a bias towards answering a question the way you think your interviewer might want to hear it. But we don't have data for that. This is simply our thinking about the study design and identifying for the Panel -- instead of just saying we might think the outcomes are underreported, at least sharing with you why we think that.

Certainly, there was a lag time between coitus and the interview. We are very respectful of data from commercial sex workers and the relevance to a study like this. We just want to point out that

because of their experience, they may be less prone to failure and -- with a device such as the female condom. And, also, it is unequivocal that they did not complete any coital logs, so there are no coital log data for that group. As I said, it's difficult to quantify the potential, if any impact, on the study. Conclusions from our review issues.

And at this time, I would like to draw your attention to Panel Discussion Question 2, which is to frame relatively generally, sort of getting at these are the limitations that we're seeing, and we are looking forward to hearing the Panel's active discussion on whether they think any of these limitations could impact the study conclusion.

And then Panel Discussion Question 3 is more focused on the actual data from the study, so quantitative results.

And, in closing, as we know, our pivotal clinical trial here didn't -- was not a contraceptive effectiveness study. However, contraceptive efficacy and STI risk reduction attributable to the Female Condom 1 have been examined in clinical studies. The acute failure rates for the two condoms evaluated in the RHRU study are comparable. And limitations in the study design raise the possibility that that

failure, acute failure rates are underreported in this study.

And, at this time, I'd like to introduce Dr. Zhang, who is going to give FDA's biostatistical presentation. Thank you.

DR. ZHANG: Good afternoon. My name is Zhiwei Zhang, and I am the statistical reviewer for this PMA. Today, I am going to discuss the RHRU study from a statistical point of view.

Here is the outline of my presentation. First, we will go over the study design and patient accountability briefly. And then we'll look at the study results and discuss their interpretation. I'll finish my presentation with a brief summary.

You may recall from previous presentations that the study enrolled 276 subjects in five subgroups and followed a randomized, crossover design. Each subject was to receive ten female condoms of each type in random order. The subjects were instructed to document their condom uses with coital logs, and they were given one coital log for all ten female condoms of each type.

When a subject finished using the ten female condoms of either type, she was supposed to return the coital log and have a questionnaire

completed at the interview. The dataset used for the analysis is based on the interviews, with or without coital logs.

This table here is about patient accountability. Overall, 84 percent of subjects made the first follow-up visit, and 73 percent did the second. The table also gives a breakdown by subgroup. The highest response rates were found in the rural family planning client group and the commercial sex worker group. The rural group lived close to the clinic, which may have helped with the follow-up. The commercial sex workers may have been encouraged by their employer to comply with the interview, although they were not allowed to use the coital logs. The student group was associated with the highest proportion of non-returners. This may be related to the study time frame, which spanned the winter vacation during which students left their institutions.

As you know, there are various failure modes for female condoms. In my presentation, we'll focus on the rates of clinical breakage, misdirection, complete invagination, and complete slippage, as well as their sum, which I call the total clinical failure rate.

This table has the estimated failure rates for FC1 and FC2 as well as their differences. This is the same table that you have in the Panel pack. In this crossover study, a subject typically used many female condoms of each type, and the outcomes of multiple condom uses by the same subject may tend to be similar. In other words, there could be within subject correlation.

One possible approach to adjust for such correlation is based on generalized estimating equations, or GEE, which is commonly used in crossover studies of male condoms. The estimates in this table are obtained from a GEE analysis with an identity link function and a working independence structure. The differences here are taken as FC2 minus FC1. So, for example, a negative difference here indicates that the estimated failure rate for FC2 is lower than that for FC1. As you can see, the estimated differences between FC1 and FC2 tend to be small and do not uniformly favor either condom type.

When we interpret the results, we should be mindful of several issues in the design and conduct of the study, which Dr. Corrado discussed earlier. So, specifically, the coital log design, we feel, was

inadequate for recording slippage and for multiple sex acts on the same day. Many subjects did not use the coital logs. The time between condom use and interview may have been too long. And, finally, there was substantial loss to follow-up.

All of these issues could have resulted in underreporting, which may be related to the observed failure rates being relatively low. These issues could also have affected the comparison of the two arms, although it seems difficult to tell, you know, how the comparison might have changed.

Dr. Corrado mentioned earlier that the study protocol contained a statement about FC2's breakage rate being lower than 5 percent. Other than that, the protocol did not specify any hypotheses in terms of the comparison of FC2 with FC1, which is the main objective of a randomized study.

With an active control in the present study, it seems natural to test for non-inferiority of FC2 relative to FC1. Here, non-inferiority means that FC2 is not worse than FC1 by more than a specified amount, delta, which represents the smallest clinically meaningful difference between two groups.

So what is the delta here? Well, there

does not appear to be a standard value of delta for comparing female condoms, which is not surprising, because there has been little discussion in the literature comparing a female condom with another female condom. In studies comparing male condoms, a 2 percent delta for each individual failure mode has been frequently adopted and widely accepted.

This is the same table that we saw a moment ago, but the focus is now on the 95 percent confidence intervals for the differences between FC1 and FC2. Whatever delta we use, we can compare it with the upper boundaries of the confidence intervals. If a confidence interval has upper boundary less than delta, then we can conclude that FC2 is non-inferior to FC1 for that failure mode. If the upper boundary of a confidence interval exceeds delta, then we cannot conclude non-inferiority.

Now, suppose we are using a 2 percent delta. Then FC2 is easily seen to be non-inferior to FC1 for each failure mode we are looking at here. In fact, the largest upper boundary in this column is 1.01 percent, which means we would be able to conclude non-inferiority for any delta greater than 1.01 percent. On the other hand, the smallest upper boundary here is 0.09 percent, which is greater than

0. With a 0 percent delta, non-inferiority is just superiority. So if we were to test for superiority of FC2 relative to FC1, the test would fail for each failure mode.

As Dr. Corrado mentioned earlier, the subgroup of commercial sex workers merit special consideration because they may have been more experienced with female condoms than the other subjects, and they may have had more difficulties remembering condom failures because of frequent sex acts and because they did not use the coital logs. So there are reasons to suspect that commercial sex workers may differ from the other subjects in terms of failure rates. To answer this question, we can exclude the commercial sex workers from the analysis and see how the results will change.

It turns out the changes are fairly small and occur in both directions, especially with respect to the treatment differences. For example, the non-inferiority criterion with a 2 percent delta is still met for each failure mode as well as the total clinical failure. So the commercial sex workers do not appear to have a large impact on the statistical analysis.

In summary, I would like to emphasize that

the low failure rates observed for each female condom may have resulted from underreporting due to problems in the study design and conduct. The available data suggests that for a 2 percent delta, FC2 is non-inferior to FC1 with respect to acute failure rates. There is no evidence that FC2 is superior to FC1 with respect to acute failure rates.

Finally, I would like to point out that non-inferiority for acute failure does not necessarily imply non-inferiority for contraception and STI risk reduction. These outcomes that represent the effectiveness for a female condom were just not observed in this study. So that concludes my presentation, and now Dr. Hesha Duggirala is going to discuss the epidemiology.

DR. DUGGIRALA: Thank you, Dr. Zhang. Good afternoon, distinguished members of the Panel and members of the audience. I am Hesha Duggirala, and I'm an epidemiologist in the Division of Post-Market Surveillance. I will be discussing the epidemiologic studies for FC1 as well as discussing the postmarket plan for the FC2 device.

The Sponsor does not provide supporting STI and contraceptive effectiveness for the FC2 device. The Sponsor relies on the FC1 literature and the

presumption of comparability between FC1 and FC2 to make a case for effectiveness. FDA conducted an independent review of the literature and found that the Sponsor's review is complete and includes all the relevant literature on female condom effectiveness.

I will be providing the Panel with summaries of the studies found on this table, including the key results and the study design limitations. FDA acknowledges that it is difficult to design and conduct female condom effectiveness studies. However, it is our obligation to note the methodologic limitations of these studies to help put the study results in context. The complete study manuscripts can be found in your Panel pack.

The first study I'll present was conducted by Trussell and colleagues. This was a clinical trial conducted in ten centers throughout Japan to assess the contraceptive effectiveness and acceptability of the Reality Female Condom. The six-month probability of becoming pregnant was 3.2 percent during typical use and 0.8 percent during correct and consistent use of the female condom.

There are a few limitations to note in this study, including that the lower coital frequency in this cohort may account for the lower risk of

pregnancy. In addition, there is no mention as to whether the sample size of 195 subjects is sufficient to compare contraceptive rates.

In the French study, women attending an STI clinic were randomly assigned to receive either female or male condoms. The groups were then followed up to assess their rates of acquiring gonorrhea, chlamydia, early syphilis, or trichomoniasis. The STI incidence rates were 6.8 in the female condom group and 8.5 in the male condom group. The authors concluded that women counseled on and provide with female condoms faired no worse in experiencing non-significant reduction in STIs compared to the male condom group.

A limitation of this study is that a subgroup analysis by the authors found that women in the male condom arm had little access to female condoms and rarely used the female condom. However, women in the female condom arm had continued access to male condoms from sources outside of the clinic, and findings from the sub-study revealed that male condoms accounted for a third of condom-protective sex acts in the female condom arm. This limitation makes it difficult to separate the effect of the female condom from the male condom, and, therefore,

it is difficult to deduce evidence of equivalence between the two groups.

The Fontanet study estimated the additional protection against STIs offered to sex workers by giving them the option of using the female condom when clients refused to use a male condom. There was a 24 percent reduction in the incidence rate of STIs in the sex establishments of the male/female condom group compared to the male condom group. The STI incidence rate decreased from 3.6 percent to 2.81 percent.

Thailand has 100 percent condom use policy that is strictly enforced, and, therefore, a limitation of this study is that results may not be generalizable to other countries where there is no 100 percent condom use policy.

The purpose of the Macaluso study was to determine whether the female condom is as effective as the male condom in preventing STI. This was an NIH-funded study and was initiated at the request of the FDA to help fill the evidence gap of STI protection following the first female condom Panel meeting.

Women attending public STI clinics participated in a behavioral intervention promoting

the female condom. The authors found that consistent and correct use of either condom was associated with a 70 percent reduction in STI rates as opposed to inconsistent use. STI incidence was lower amongst consistent users who mixed condom types than among exclusive male condom users. The authors concluded that consistent condom use reduces STD risk but incorrect use and condom failure may greatly reduce effectiveness. They also concluded that the female condom appears to be at least as effective as the male condom as a barrier to STI.

A significant limitation of the study was that one group received a supply of male condoms and the other group received female condoms with male condoms as a backup. This type of design fails to separate the effect of the female condom from the male condom and therefore cannot provide any evidence of equivalence between the two groups.

In the study by Hoke and colleagues, sex workers in Madagascar were followed to assess whether adding female condoms to male condom distribution led to increased protection levels and decreased STIs. For the first six months, participants had access to male condoms only. In the final 12 months, they had access to both male and female condoms. Aggregate

STD prevalence declined from 52 percent at baseline to 50 percent at month six. With the female condom added, STI prevalence dropped to 41 percent at 12 months. The authors concluded female condom introduction is associated with increased use of protection to levels that reduce STI risk.

The longitudinal design makes it difficult to assess whether increased knowledge and awareness after the male condom phase may have influenced the female condom phase results.

The objective of the Feldblum study was to measure the impact of the female condom on STI in Kenya. The investigators found no difference in the prevalence of STIs during follow-up at the intervention versus the control sites. The Sponsor in the PMA asserts that the female condom findings were favorable for this study. However, the investigators concluded that the female condom introduction did not enhance STI prevention at these sites.

A limitation of this study, which was found in many previous studies, is that the study's design did not distinguish between the influence of the female condom versus the male condom.

The Sponsor in their PMA provides a few

examples of studies that do not look at FC1 effectiveness but more on acceptability. These studies do not appear to be relevant to the effectiveness of the female condom and will not be discussed further here.

I will now discuss the postmarket plan for the FC2 device. The Sponsor has provided information on the post-approval evaluation of this device. All procedures, as stated in the Quality Systems performance standard for all PMA devices, will be followed for release of this product, including recording all customer complaints, as well as following MDR and product-recall requirements. In addition, the Sponsor will provide a summary and bibliography of unpublished reports of data from any clinical investigations or non-clinical laboratory studies involving the device and reports in the scientific literature concerning the device.

The Sponsor has not proposed a post-approval study. Please note that post-approval studies are used to evaluate long-term, real world uses of medical devices. Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

The plan to conduct a post-approval study, if decided upon, does not decrease the threshold of evidence required to find the device approvable. The premarket data submitted to the Agency and presented in this Panel pack must stand on their own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable. FDA uses premarket clinical data to develop post-approval studies. Based on the limited clinical outcome data in this PMA, we are unable to develop such questions.

The literature presented shows a trend towards risk reduction associated with use of the female condom. From an epidemiologic perspective, the effectiveness literature on FC1 has methodologic limitations. It is important to note that these studies are difficult to design to account for potential confounders. In addition, there is no epidemiologic effectiveness data on FC2, the device under review.

Typically, FDA uses premarket clinical data to aid us in generating postmarket questions. This PMA does not have such clinical outcome data, and in the absence of that, we cannot generate these post-approval questions. If this device is deemed

approvable, the Panel may recommend that the labeling for FC2 explain that the effectiveness of the FC2 device has not been evaluated for STI and unintended pregnancy protection. We look forward to the Panel's discussion on the appropriate postmarket evaluation of this device. Thank you.

DR. CEDARS: Thank you. I'd like to thank the FDA for their presentation and open up for questions from the Panel to the FDA. Dr. Padian?

DR. PADIAN: I need to get a clarification. I think I should probably know this, but the female condom, FC1, has an STI indication on it, right? But the data that you looked at when they did the pivotal study was only pregnancy, right? So I mean, what I'm having a hard time getting my head around is that, on the one hand, you don't want to infer -- I understand that there's this sort of reluctance to -- should I stop before I go on? No, because they -- they're, like, they're becoming --

UNIDENTIFIED FEMALE SPEAKER: We're just wondering to whom you're addressing the --

DR. PADIAN: FDA guys --

DR. CEDARS: This is to the FDA, this is to the FDA.

DR. PADIAN: I'm not sure which one of you.

And so do you already know what I'm -- do you know what I'm asking?

MR. POLLARD: No. I'll let you crystallize your question.

DR. PADIAN: Personalize it?

MR. POLLARD: Crystallize --

DR. PADIAN: Oh.

(Laughter.)

DR. PADIAN: No, Colin, I don't know you that well. But so, I mean, on the one hand, there seems to be a reluctance to infer from any kind of equivalence from FC2 to FC1 both STI and pregnancy, but, nevertheless, decisions were made regarding efficacy for STIs for FC1; some sort of inference was made based on pregnancy, or so it seems. And then I have a follow-up question.

MR. POLLARD: Yeah, I'm not sure what you mean by reluctance. We're putting this question to the Panel for discussion. But, certainly, the primary point you're making is that, certainly, indeed, in 1993, was our approval of it. We approved it knowing we didn't have that STI risk reduction data. We had this mitigating labeling that we felt went to some degree towards that, and sort of as another part of the bargain, our FDA commissioner

actually went to the NIH director and specifically asked them to help address this evidence gap. So I mean, that's --

DR. PADIAN: Okay. No, that puts it in context. Should I not ask my other one and come back to me later?

DR. CEDARS: Go ahead and ask yours and then we'll go to --

DR. PADIAN: Okay. And my other question has to do with the interpretation of the literature, and, here, too, I might be getting it wrong. And that is it seems to me your ability to extricate the -- to attribute what you see to male condoms and female condoms sort of has to do with what your research question is, because if your research question is -- and I'm not sure. That's why I'm asking. If the research question is that the addition of female condoms increases protected acts, which you might be able to address in labeling, that would be different than if your research questions were equivalence. And I think about all the prevention studies going on now with microbicides and diaphragms. All of them have male condoms that are part of the drill.

DR. DUGGIRALA: Yeah, and so that is two

completely separate questions --

DR. PADIAN: Right.

DR. DUGGIRALA: And that's something for the Panel to keep in mind in terms of their evaluation of this device. Are we looking at something that just enhances overall protection by adding it to the mix or are we actually looking at --

DR. PADIAN: Right.

DR. DUGGIRALA: -- what is the effective of FC1. And so that's something for the Panel to consider in their discussion.

DR. PADIAN: Okay.

DR. CEDARS: Dr. Zenilman?

DR. ZENILMAN: I have two questions. One is --

DR. CEDARS: Could you please use the microphone?

DR. ZENILMAN: Okay. Sorry. Two questions for the FDA. One is there was no mention in your presentation on the use of surrogate markers, and what your sense is on the value of a surrogate markers. The two papers that were in the packet, one of which was authored by Dr. Warner, suggests that PSA is detectable in between 15 to 25 percent post-coitally, which is actually substantially higher than

the male condom, which actually raises some issues. Actually, we've done some studies in male condoms which actually show that the rates are much lower using a different marker.

The other question is actually regarding not labeling but promotion. I think one of the -- in all of the presentations this morning, we heard how important this is for HIV prevention and STI prevention, and, yet, there's no data to actually -- outside of maybe aspirational data, that it actually works. And I know it's not specifically in the label, but I'm wondering if you can comment on this. I mean, my experience is more in drugs, and I know that -- I'm not sure what the regulations are. Actually, my experience from drugs was that the drug reps can't mention anything that's not, you know, that's not in the package insert. And I'm not sure if the rules are different for devices.

MR. POLLARD: So your first question had to do with other potential markers?

DR. ZENILMAN: Right, surrogate markers, recognizing the difficulty in using STI --

MR. POLLARD: Right, like a semen biomarker is what you were talking about?

DR. ZENILMAN: Right.

MR. POLLARD: And, you know, I think -- I tried to touch on that a little bit at the very beginning this morning where there is some very interesting work going on in this arena, but when we looked at it carefully, we didn't feel like the methodology itself had been adequately validated at this stage. People are continuing to work there, and it does look promising.

The second question, can you just --

DR. ZENILMAN: The second question was, you know, what are the rules in terms of promotion and labeling for indications which aren't supported by the data? I mean, the only -- there's an STI indication, which is based on --

DR. CEDARS: Labeling is one of the issues we're going to be discussing. Is that not after --

MR. POLLARD: Certainly, that's something that I -- is that really what you're asking?

DR. PADIAN: Sort of related to mine --

DR. CEDARS: It's related to Nancy's question.

DR. PADIAN: Yeah.

DR. ZENILMAN: Yeah.

DR. PADIAN: Which is you put it on the label, but there weren't data?

MR. POLLARD: Yes, that's right. However, I mean, you know, the labeling does say what we do know, and we were making some inferential judgments at that time.

DR. ZENILMAN: Um-hum.

MR. POLLARD: And, to be honest, as we were very sort of clear about, you know, one of the questions we're asking you, you know, maybe the key question that this PMA's about is slippage and breakage, invagination, misdirection. Those are the failure modes that we recognize to the best of our degree with female condoms. Isn't that enough? Do you have to -- do you have to do a contraceptive study?

DR. ZENILMAN: Um-hum.

MR. POLLARD: Do you have to do STI risk reduction --

DR. ZENILMAN: Okay.

MR. POLLARD: -- studies to establish that the product's safe and effective with reasonable assurance.

DR. CEDARS: Dr. D'Agostino?

DR. D'AGOSTINO: The presentations, I guess, were done in such a way that you didn't want to let out how you feel about things and leave it all

to us, but I was surprised, for example, with the dropout rate. Being so large, what did -- actually in line with the questions that are being asked now, in devices, you don't worry about the dropout? I mean, it's 27 percent. Aren't you worried that they may not be showing up because they're having failures and they're really fed up with -- moving to other things --

MR. POLLARD: Yeah, that's part of Panel Discussion Question Number 2.

DR. D'AGOSTINO: So you didn't want to lead us? And the other question -- another question I had is that if you break it down to the per subject, which is really where the exposure would be measured, did you notice anything between the Phase 1 and Phase 2 of the crossover, because many times in crossovers, after you do the Phase 1, going on to Phase 2 is just useless because they've learned out to --

MR. POLLARD: I would suggest that get directed to the Sponsor.

DR. D'AGOSTINO: Fine. Do they --

DR. CEDARS: Well, let's finish the FDA questions first, and then we'll have the Sponsor come back. Dr. Thomas?

DR. THOMAS: In designing these type of

studies and coming up with the different failure modes, I mean, especially when you're comparing the female condom potential failures to male condom, the one area that wasn't mentioned that I think sometimes is important when it comes to invagination is leakage. Was leakage data captured? Was that looked at in any way, shape or form, or it just wasn't thought to be as important?

DR. CAREY-CORRADO: So let me just make sure that I understand. Are we talking about leakage of semen outside the condom? Okay. And it's our understanding that those data were not collected in this study, that the data that were collected officially were all based on a interview and that, as I understand it, there were no assays done or any effort to collect data on what semen exposure might have -- what the degree of semen exposure might have been in the vagina. But, of course, I have to defer to the Sponsor because they will be in a better position to answer that definitively.

DR. CEDARS: Dr. Marzano [sic]?

DR. MARRAZZO: Oh, sure. I have another question about feelings. Maybe it's not the right way to ask it, but it goes back to both Nancy's and Dr. D'Agostino's questions. So the proposed

indication for use does include the phrase "helps to prevent HIV/AIDS, other STIs, and unintended pregnancy." And I understand that the study that you described, Colin, I think the Macaluso study was the one that was done to address the evidence gap, and that study did show the 70 percent reduction with the caveats that you mentioned. What was the FDA's feeling in response to that? Was that adequate? Was there thought about getting more evidence to maintain the indication for -- I mean, what -- how did the FDA respond to that? It seems to me a critical question.

DR. CAREY-CORRADO: I can take a stab at that, and I guess what I would say is that FDA considers that the indication for use for the FC1 can stand. However, at the same time, we didn't think that data from any studies we've seen to date lead us to believe that there's reasonable assurance that the degree of STI risk reduction for the female condom is as good as that of the male condom. And that's the reason that our position has been that we believe the four statements that occur on the FC1 labeling should remain if this were to be approved; that is to say, use a male condom. That should be your first choice. However, if you're not, then we do believe that there is some risk reduction that can be obtained from the

FC.

DR. CEDARS: Dr. Ramin?

DR. RAMIN: One question I had was for the FDA is on the patient accountability slide, where you look at the loss to follow-up. Do we know specifically how many of the patients were randomized to the FC2 -- we didn't get the follow-up data on?

DR. CAREY-CORRADO: That's a great question, and, no, I do not know at this time. I would have to look back into the PMA to figure out if loss to follow-up -- as I recall, they started with 276, so they ended up with 233 at the first visit, and that's 276 minus 233, I think is -- it's either 33 or 43, and then between the first and the second follow-up, it was 233 minus 201, so that's an additional 32. So a few more were lost to follow-up between enrollment and the first follow-up visit, but in terms of how that reflected distribution into which they were going to use first, I do not know.

DR. CEDARS: And the last question for the FDA, Dr. Stubblefield. There will be opportunity to ask questions during the discussion phase of both the FDA and the Sponsor. Dr. Stubblefield?

DR. STUBBLEFIELD: I don't recall any discussion either by the Sponsor or by the FDA of the

viral studies, which, according to the FDA's executive summary, show that the FC2 failure rate is acceptable because it's comparable to that for male condoms and it's lower than that for the FC1. The 5 percent was the failure rate for the FC2 in the male condom and 15 percent for the FC1. It seems to me that's important information to talk about.

DR. CEDARS: I think that we'll have the Sponsor answer, but is that in any way reassuring to the FDA in terms of STI protection? I mean, it's an in vitro assay, but is that any way reassuring or do you have any comparators that would make that reassuring?

DR. CAREY-CORRADO: That wasn't my review area, but I can say we definitely weigh the value of well-designed bench studies that describe the, you know, whether or not the material is permeable. Now, again, this wasn't my review area, so I'm not sure if that's specifically what Dr. Stubblefield is referring to.

DR. CEDARS: Yes.

DR. CAREY-CORRADO: But permeability data, bacteriophage data, yes, we absolutely look at that. And it certainly does provide -- it does constitute valid scientific evidence that can contribute to our

decisions.

MS. BLYSKUN: Yeah, and I would just add the comparators, at least for male condoms, we typically look for a male condom control for this type of study.

DR. CEDARS: Okay. I'd like to thank the FDA, and if we could have the Sponsor initially with Dr. Taylor come back up to see if he found any additional data about the loss to follow-up. And then if there were some residual questions that are important before we get started on the discussion issues for the Sponsors, if we could ask those. And, then, again, once we get started on the discussion questions, there will be an opportunity to ask either the FDA or the Sponsor additional questions.

DR. TAYLOR: All right. Thank you. I think there were two questions. One was initially the issue about the high loss to follow-up and whether -- I had mentioned something about comparing the rates among people who completed both groups. I do not have those data available, so I can't tell you what the answer to that is.

DR. CEDARS: Did you look at in the -- where there was closer to 75 percent follow-up, and this would get a little bit to Dr. D'Agostino's

question about which they used first, and since they were randomly assigned for FC1/FC2, did you look at the completion, FC1 versus FC2 at Visit 1?

DR. TAYLOR: Yeah, that's all in Volume 2 of the Panel pack, Table 6(a) and 6(b). Table 6 gives all the results overall. Table 6(a) gives the results at the first follow-up visit, and Table 6(b) gives all the results of the second follow-up visit.

DR. D'AGOSTINO: Can you remind us what it says -- I mean, I --

DR. TAYLOR: If you turn the computer this way and look, I was just trying to do that. The total clinical failure rates, the 95 percent confidence interval is, I'm guessing -- the upper bound is 2.4 percent in the first follow-up, and it's less than 1 in the second follow-up. But I really --

DR. CEDARS: The upper bound in the 95 is a positive 2.5?

DR. TAYLOR: 2.43, yes.

DR. CEDARS: So it's over the cutoff of 2?

DR. TAYLOR: Well, 2 is -- for one, it's half the study size, so you're going to expect wider confidence intervals, and 3 is what the FDA had mentioned for actually for female condoms. But, in any case, it is over 2. It's 2.4. And for the

second period, it was under 2.

DR. D'AGOSTINO: I'm pondering the generalizability of the study. There was counseling, right?

DR. TAYLOR: I should put a caveat here. My role in this study was to evaluate --

DR. D'AGOSTINO: Well, somebody there was counseling, right?

DR. LEEPER: Mags --

DR. TAYLOR: Having to do with the study, Mags is the person --

DR. D'AGOSTINO: Yeah, so there was counseling. Then, you know, when did the failures happen? And then they come back so -- and you switch over. So I'm wonder, you know, just can -- did you do so many things to these individuals that maybe we can't generalize the study? I mean, are people going to -- females in the States always going to get counseling?

MS. BEKSINSKA: Well, I think in the study context, people do get probably much more --

DR. D'AGOSTINO: I know. But then --

MS. BEKSINSKA: And in the clinic setting, women are informed right at the start of use. They get much more information on the female condom

because normally they haven't used them before and it's a new device. So they do get a great deal more information. But, obviously, in the study context, they probably get -- in all the studies on female condoms.

DR. D'AGOSTINO: Well, it would be very interesting, you know, given advice, this counseling, deliberate counseling, and in the first phase of the crossover, that you exceed the non-inferiority margin; then by the time you go to the second, everybody is sort of trained and what have you and doing well, and then the rate drops below the two, the upper confidence bound. So it's very hard to know if you can put all that together -- added that to the fact that there's a lot of missing data of people who probably -- my sense always when people don't come is because things aren't happening the way they want them to happen.

MS. BEKSINSKA: Yes, I understand.

DR. D'AGOSTINO: And so the rates may be much higher.

MS. BEKSINSKA: I think it's natural to assume that the women -- I mean, the women in the acceptability section all say it gets easier with practice, so I think that came up often that, you

know, if you use one, two, or three -- in fact, even in the instructions available now, it says maybe try a few before you actually even use them. So, certainly, there's a practice effect.

DR. CEDARS: Thank you. If there are other key questions? Dr. Katz? For the Sponsor?

DR. KATZ: Yes. To follow-up on your last comment on acceptability, I wonder if you could just -- I guess, Mags, this is probably for you. If you could just summarize for us the salient findings on acceptability.

MS. BEKSINSKA: Can you just give me a minute, and I'll just pick a few key things out of the paper I've got in front of me.

DR. KATZ: Okay.

MS. BEKSINSKA: Give me two minutes and I'll --

DR. CEDARS: Dr. Padian?

DR. LEEPER: While she's looking at that, Dr. Whang, if you go to in your PMA pack, Figure 1, Page 208, and it shows a flowchart. Maybe you can get --

DR. WHANG: It's in Volume 2, Tab 1.

DR. LEEPER: Thank you. Volume 2, Tab 1 says the number of screened women equaled 289. Then

the number of women enrolled was 276, and then it was divided up in the two groups. You're going to find it?

UNIDENTIFIED FEMALE SPEAKER: Yes.

DR. LEEPER: Okay. We're going to find it and put it up on the screen. But basically -- let's wait until it gets up on the screen.

DR. CEDARS: Dr. Padian, do you want to, while they're looking for that, ask your question?

DR. PADIAN: Yeah, I think this is a pretty easy question. I'd like to get back to the coital log and multiple female condoms used on the same day. Correct me if I'm wrong, the only way you could get that information if you used multiple condoms on the same day was from the coital log, is that correct?

DR. LEEPER: That's correct.

DR. PADIAN: And so it might be the case that sex workers would be the ones that would be most likely to use them, to use multiple ones, and those are the very ones for whom we don't have the data.

DR. LEEPER: Multiple sex acts on a given day --

DR. PADIAN: Yeah.

DR. LEEPER: Correct.

DR. PADIAN: Okay.

DR. LEEPER: And the students as well. Also --

DR. CEDARS: So can Mags just clarify that? Is that, in fact, true that the only way you got information about multiple sex acts on the same day was from the coital logs because that seemed to be in conflict. I had a question about that as well, about what you said.

MS. BEKSINSKA: Well, the multiple sex acts were on the coital log, but in the questionnaire, we didn't ask about multiple sex acts on the same day.

DR. CEDARS: So, again, it is true, the sex workers who were most likely to have multiple coital acts in the same day --

MS. BEKSINSKA: Multiple sex --

DR. CEDARS: -- who had no coital logs, that data was not gathered?

UNIDENTIFIED FEMALE SPEAKER: But it can't be just the sex workers --

UNIDENTIFIED FEMALE SPEAKER: It's the students --

UNIDENTIFIED FEMALE SPEAKER: -- because that was half of their total subjects that had more than one coital act on the same day.

DR. PADIAN: No, correct, but the ones most

likely are probably the sex workers --

DR. CEDARS: And the students --

UNIDENTIFIED FEMALE SPEAKER: Well --

DR. CEDARS: Okay. Do we have -- so this table -- can we -- is this the table you wanted? Oh --

DR. WHANG: Can I just share that it's also in the executive summary that the Panel members --

UNIDENTIFIED MALE SPEAKER: Yeah.

DR. WHANG: -- received on Page 38.

DR. CEDARS: Yay Dr. Whang. Okay, yeah, but this has the total numbers. It doesn't have the failure rates attached to it, which is what I think people were asking about.

DR. WHANG: I think you can see -- I think it indicates the difference of the loss to follow-up depending on the original randomization, but I'll let the Sponsor speak to that.

DR. LEEPER: Okay. Mags, do you have the answer to that question?

DR. CEDARS: Okay. The issue about the acceptability.

MS. BEKSINSKA: Okay. Just some key issues. For 27 percent of women said in FC1 and in FC2 that it got easier with practice. The ease of

insertion for FC1 was 58.7 percent as easy and 57.5 as easy for FC2. Difficult to insert, the opposite end, was 4.6 in FC1 and 2.8 in FC2. But when we kept asking these questions, often the response we got, instead of easy, moderate, difficult, was everyone was saying the first response was it gets easier with practice. So it's actually quite difficult I find with these questions because, you know, they'll say, "Well, the first three were difficult, or I found the first three not comfortable. Then the last few were comfortable."

For the amount of lubricant, 60 percent felt it was just right in FC1, and 62 percent felt it was just right in FC2.

For the size, 26.1 percent of women for FC1 felt it was too big, and 73 percent felt it was the right size. And for FC2, 28 percent felt it was too big, and 71 percent felt it was the right size.

I don't know if you want -- the general feel of the condom, that they liked the general feel of the condom for FC1; 63.3 percent said they liked it, and 33 percent said it was okay. For FC2, 60 percent said they liked it, and 36.1 said they felt okay.

Many of the acceptability issues were

almost identical. In fact, some women actually said at the end they couldn't tell the difference between the two condoms. And definitely with the partners as well. It was very similar for -- the similar issues, partner issues.

So the partner said for FC1, 29 percent for both felt it was natural. For the size and not too tight, for FC1, 29 percent said that; 15 percent said that for FC2. For the strength of the material, 16 percent of men felt it was strong in FC1; 22 percent said it in FC2. So this was the open-ended qualitative section.

DR. CEDARS: Thank you.

MS. BEKSINSKA: I don't know if that's enough.

DR. CEDARS: Thank you. Ms. George, do you have any questions?

DR. LEEPER: Can we go to this chart? We never finished Dr. Whang's question. Mags, stay up there. Are you finished with this chart, Dr. D'Agostino? Did you want any -- does this help you at all?

DR. D'AGOSTINO: No, well, it does in some sense that you have 20 percent who started it off with FC2 didn't finish the first period and only 11

percent who started off with FC1 finished the first period. So, I mean, are the 10 percent dissatisfied with FC2 and just didn't come back and tell you anything about it?

DR. RAMIN: So I calculate 44 women did not come back after the FC2, if you add them all up --

DR. D'AGOSTINO: What's that?

DR. RAMIN: Forty-four women.

DR. D'AGOSTINO: Yeah, but 133 were assigned to FC2 --

DR. RAMIN: And 106 followed up.

DR. D'AGOSTINO: Only 106 came back to report on it.

DR. RAMIN: Right, so that's 27. And then if you go down to the left side --

DR. D'AGOSTINO: So that's 20 --

DR. RAMIN: -- 127 were assigned.

DR. D'AGOSTINO: That's 20 percent who didn't finish the FC2.

DR. CEDARS: But at 0.1.

DR. RAMIN: At 0.1, right.

DR. D'AGOSTINO: Yeah.

DR. CEDARS: Okay. Thank you.

DR. LEEPER: Did you want --

DR. CEDARS: Do we have other questions for

the Sponsor, and then we need to go to the discussion.

DR. LEEPER: I've got a couple --

DR. CEDARS: Yes?

DR. LEEPER: I would like to make a couple clarifications at least just for myself. First of all, Mags, do you want to talk any more about the people who did not come back?

MS. BEKSINSKA: No.

DR. LEEPER: No? Okay. Then could we go back to the question about multiple sex acts so that I'm clear about what your concerns are about that? When we talked about the multiple sex acts and we looked at the coital logs, because on the coital logs, they're recorded that they had multiple sex on one day whereas if they just went back for the interviews and they didn't use the coital logs, then it just had to come out in the discussion as to whether or not, you know, what the failures were. And we went through the, you know, there was 194 failures, of which 84 had not been reported on the coital log. I'm trying to figure out what -- I want to answer the question around multiple sex acts, and I'm sorry, I don't understand the specific question.

DR. CEDARS: Well, I think the concern was

that you were saying that multiple sex acts were only encountered or only captured off the coital log, and, yet, the people who were most likely to have multiple sex acts didn't keep a coital log. And so the question was, was there underreporting of events or episodes in the people most likely to have multiple sex partners and multiple sex acts in a given day?

DR. LEEPER: Right. And that would be the same issue whether it was multiple sex acts on a given day -- the issue goes back to was the failure identified, whether it was a single sex act or a multiple sex act day? The key question is was the failure identified. And what our whole position has been is that for those who did not use the coital logs, which was 63 percent were commercial sex workers, were we able to elicit whether or not they had a failure? And we did that in the interview process. And that's how, you know, that's how we found out, yes, they did or no, they didn't. There were 84 additional problems that were identified through that interview process.

DR. CEDARS: Thank you.

MS. BEKSINSKA: Can I just make a comment on the multiple sex acts. In our population, and if you look at our sociodemographic characteristics, in

this study and other studies, most women are actually not married or living with their partner. So when you look at coital logs in our studies, you find that sex especially is concentrated around the weekends. Women don't have sex during the menstrual cycle, but if they are not married or cohabiting, they tend to see their partner on weekends, so we often find that multiple sex acts are clustered for all women around sort of Friday, Saturday, Sunday, and then there's very little during the week. So that's just one reason why we have so many sex -- especially with the students as well. They see their partners at weekends.

DR. CEDARS: Thank you. So one more question from --

DR. DAVIS: Well, just my concern about this goes back to Table 10, that there was much more -- appeared to be much more breakage, nine events, in the patients or the subjects with greater than one condom used in a day than in FC2 compared to FC1. The breakage was much -- appeared to be greater.

DR. LEEPER: Which table is that? Sorry.

DR. DAVIS: Back to Table 10 again.

DR. LEEPER: On page what of what?

DR. DAVIS: Forty-three on ours.

DR. CEDARS: Oh.

DR. LEEPER: That's the FDA table? FDA Table 10?

DR. CEDARS: That's the FDA data.

DR. DAVIS: Yeah. Oh, and Nancy --

DR. CEDARS: Okay. Doug could you look at that?

DR. DAVIS: That's why I was concerned about these multiple acts.

DR. CEDARS: That's the FDA table.

UNIDENTIFIED FEMALE SPEAKER: Oh, the executive summary?

DR. CEDARS: Yeah, they --

MS. BEKSINSKA: But if we look at the total breakage, all the breakages, we find that there's actually very few breakages where there's more than one breakage. So we're talking about a handful of women who actually had more than one breakage.

DR. CEDARS: Okay. Dr. Corrado, did you want to add anything to that?

DR. CAREY-CORRADO: Right. I put the table together. I compiled it from a response that the company sent us when we were really trying to get

down into the issue of how many failures. The point was that we were concerned that on days of multiple acts, that the failure number had to be a minimum because the coital log wasn't designed to put in a number in those little boxes next to each failure. So our question was how bad could it have been? If this really was a problem, how bad might that problem have been?

And so in Table 10, these data come exclusively from the coital logs. And, yeah, I mean, when you just look at the raw numbers, you do see especially, for example, for break, three reported for FC1, nine for FC2. The caveat that I had was that there were some additional breaks in each of those groups if you include breaks that occurred as part of a combination of failures.

But, nevertheless, you know, this -- the numbers in this table, you know, they stand. Now, I also want to add that sometimes during the interview, the data that was in a coital log might have been in some way, and I'm using -- I'm thinking of the word sensor -- that might not be exactly the right word. But all of these failures that you see here, as recorded on a coital log, might not necessarily have made it into the questionnaire as I understand that

exercise. Again, just restricted to coital log and doesn't include combination failures.

In the original PMA, actually, there is a slightly different set of numbers, and non-clinical breakage apparently skewed the numbers against the FC2 in the PMA data. But, again, although the numbers are small across all these databases, you know, they're -- the numbers are very small, and it might appear, you know, that there is an important difference, and given the small numbers, I'm not so sure if we can say that. So I don't know if that helped or not, but I'm --

DR. CEDARS: Thank you. And I think Dr. Taylor may have a response.

DR. TAYLOR: Yeah, I just want to mention that there's also a Table 11 that looks at essentially the same thing on events where a failure occurred when only one sex act occurred on the day, and you don't see that. So I'm not saying -- all I'm saying is we really are digging pretty deep into the data when we start looking at these types of things. And, in fact, if you look at Table 10, the proportion of people who -- because I don't have it in front of me -- the overall failure rate is --

DR. CEDARS: Is equivalent --

DR. TAYLOR: -- lower in FC2 than FC1, and, in fact, there's a big difference in I think the invagination or is it the misdirection --

UNIDENTIFIED FEMALE SPEAKER: Invagination.

DR. TAYLOR: -- which flips the other way. Now, which is more important, invagination or -- I mean, I don't know. I'm just saying it is digging very deep into the data, so we need to keep that in mind.

DR. CEDARS: Thank you. Dr. Peterson, do you have a comment before we go to the questions?

DR. PETERSON: Just one before the discussion. It seems like there are two concerns the FDA has raised that are related on reliance on the interview and potential for underreporting. And it wasn't explicit, but it seemed implicit that the concern is not differential misclassification but non-differential misclassification and biased toward the null such that the lack of differences is because of the underreporting. And the link with the interview, then, seems that there's a question still outstanding about whether or not the -- how the interview and the coital logs were used.

And Dr. Leeper's remark just now helped me in seeing that there's more of a link than I had

heard. And Dr. Beksinska said that the coital log was used as a prompt in the interview. So could we hear a little bit more about how -- when we see an outcome, breakage, et cetera, what trumps what?

If there were three breaks on the coital log and one on the interview, the coital log and the interview, that would not be possible because the interviewer would say, well, there are these three breaks in the coital log. Let's talk about those three breaks, versus the interviewer says, "Did you have any breaks," and, "Yeah, I had one." And say, "Well, gosh, the coital log has three. Can we talk about" -- so how was the final outcome measure determined?

MS. BEKSINSKA: Okay. Okay. So if someone came with a coital log and they had a number of failure events on it, the -- so if a woman put down that she had had an invagination, for instance, she was still asked the question about invagination because, for instance, for invagination, we used a question to break down whether it was partial or full. And, in fact, there was one or two women who said, well, the condom moved, and then we had to work out if she didn't put it on the log, whether there was an event that happened. And there were some

extra events from discussing with women in detail that something did seem to have happened. So we erred on the side of caution, and we actually recorded some extra events that weren't on the log, even women who came -- the log.

So, for instance, if we, you know, if she had three breakages, we would discuss those breakages, and for each breakage, she has a chart where every single breakage -- we ask the detail on those individuals breakages, whether it was clinical, whether it was non-clinical, when it happened. So even for non-clinical breakages, we know whether she did it with her nails or whether she opened the packet with a pair of scissors, when that breakage was discovered, so, for instance, whether it was during sex or whether it was after sex and on removal.

And we erred on the side of caution. And if she wasn't sure when it was broken, we automatically put it as a clinical breakage, not a non-clinical breakage.

DR. PETERSON: Can I just follow up?

DR. CEDARS: Yeah.

DR. PETERSON: So the interview was really structured around the coital log to some extent?

MS. BEKSINSKA: Yeah.

DR. PETERSON: So it wasn't that she was asked the question, "Did you have any breaks," in isolation. The coital log was in front of both of you, or the interviewer, and said, "Gee, I see you had three breaks. Let's talk about those" --

MS. BEKSINSKA: Yes --

DR. PETERSON: -- as opposed to just not looking at that and saying, "How many breaks did you have," and then having to reconcile?

MS. BEKSINSKA: Yeah. So it was there and so it was -- the questions were about that, but then other things came out in the discussion, extra came out.

DR. PETERSON: Okay.

DR. LEEPER: If we could look at this table that we have up here on the chart, on the screen, if you look at the first half -- can I have the pointer? If you look at -- okay. If you look at this part, over here is the total, and then it's broken down FC1 and FC2. What we tried to do is, okay, how many problems were reported on the coital log. And then they scrubbed out those problems on the coital log, and they identified problems that were perhaps mis-catalogued on the coital log. Like Mags just said,

well, maybe it really wasn't invagination. Maybe it was misdirection. And so we pulled that -- we identified the problems that were on the coital log that were not correct. We added the problems that were on -- that were not on the coital log but identified through the interview process so that we could nail down exactly what happened during the use of the female condom during that sex act.

And in that process, we went through, and you can see the totals on the bottom for each one of the questionnaires. And there were basically a total of 194 problems of which 84 of them were identified through the interview process. And 34 of those were identified through the interview process that had not been on the coital log.

MS. BEKSINSKA: I'd also like to add there were some problems noted on the coital log that we then removed. So, for instance, for invagination, a woman may tick that the condom was pushed inside, and then you talked to her, and she says, "Well, you insert it inside, so of course it's pushed inside." Or we say to her -- we ask women to clarify then if the ring was inside the vagina. So some women said, no, the ring hadn't gone into the vagina, but the condom felt it had pushed in a little bit. But it

was still outside. The ring was still outside the vagina, but they felt it had been inserted a little bit further, just the material. So there we actually wrote down that this was not an invagination because an invagination is when the condom is pushed into the vagina.

So we actually had quite a difficult time. We had, because of the definition, to clarify exactly what happened. I don't know if you understand that, but that's, you know, so we did actually take off some things that we felt were not failures.

DR. CEDARS: Thank you. We need to cut this discussion short. We get back to the coital logs in Question Number 2, so we do need to move on to the Panel discussions. So if I can have the Sponsor go back to their seats, and if we can put Question 1 up on the slide for the Panel members? You have all the questions in your packet.

The first question has to do with whether or not a contraceptive effectiveness study is done. I won't read the whole question. But the Sponsor's assertion is that the study shows FC2 is functionally equivalent to FC1 and then therefore would be just as effective in preventing pregnancy, HIV, et cetera, and other STIs.

And so what we'd like the Panel to discuss is whether the acute performance outcomes, breakage, failure modes, et cetera, provides reassurance about safety and efficacy for the female condom. I would like to open that for discussion.

DR. STUBBLEFIELD: Can I ask a question by way of beginning the discussion?

DR. CEDARS: Please.

DR. STUBBLEFIELD: I believe it says in the executive summary that in the case of the male condom we do -- FDA does go along with exactly what the Sponsor is asking for this condom, for the female condom; namely that a new condom has -- if it's shown to be equivalent in terms of these tests, then we accept that it is efficacious without insisting that the new condom manufacturer undergo efficacy testing?

DR. CEDARS: I think that that's true --

DR. STUBBLEFIELD: Yes.

DR. CEDARS: That's my understanding. And I think the difference may be that condoms are Class II where as the female -- or male condoms are Class II whereas the female condom is a Class III product, device, is that correct? And that's why the question is raised here. And so part of our discussion question is should there be an equivalency between

those two. Is that correct from the FDA?

DR. WHANG: Right. So for this female condom, as we understand it, is an acute performance outcome study, that is, a failure mode study, is that an adequate method for demonstrating a reasonable assurance of safety and effectiveness for this female condom?

DR. CEDARS: So I think that your first opening question was exactly part of the issue that we're trying to get at, whether we can use this in the way that a male condom study would be done. Dr. Warner?

DR. WARNER: I have a follow-up question to that, and that is if we're asked to judge whether this Class III device can be evaluated with Class II criteria, what precedent does making that exception have for other Class II or Class III devices?

DR. CEDARS: Well, or can I ask it another way. What precedence would it have -- well, one is, can you do that with a Class III device; and, two, would it have precedence for other Class III devices or would it have precedence for other female condoms?

DR. WHANG: I don't think we're calling this a Class II type of study. I mean, it is a type of study, a failure mode study that is currently used

for some Class II devices, male condoms. But if it were acceptable here, this is still a Class III device, and it's a type of study we would be deciding is okay for some Class III devices. No, we are deciding it for specifically for this female condom if you were to recommend that a failure modes analysis is adequate for this female condom. It wouldn't necessarily have to apply to all female condoms.

DR. WARNER: Or all Class III devices?

DR. WHANG: Correct.

DR. CEDARS: Okay. Thank you.

UNIDENTIFIED FEMALE SPEAKER: That is a good question.

DR. CEDARS: Other questions, comments, discussion for this issue because I think this is perhaps the most critical. Questions 1 and 2 I think are the most critical for discussion.

Dr. Gilliam?

DR. GILLIAM: I'm just struck by how valuable the in vitro studies are here and how few questions we have, and then when we look at the actual use study, we are going a little bit out of our minds trying to judge the quality of the data. I could imagine if we were trying to look at STIs and

pregnancy, it would be even worse. So I think this -- we get very good data in this way especially from the --

DR. CEDARS: From the in vitro studies?

DR. GILLIAM: From the in vitro studies.

DR. CEDARS: Dr. Padian?

DR. PADIAN: I also agree with the comment that -- I think it was Dr. Taylor that made this point that, in fact, I think it's highly likely that if we did a contraceptive -- with pregnancy as an outcome, that a lot of that would be actually attributed to non-use as opposed to failure, and it might be difficult to separate that out.

DR. CEDARS: Dr. Katz?

DR. KATZ: I think if we look -- is this on? Yes. I think if we look at the structure of the decision-making exercise that we are going through, we cannot escape the fact that neither the in vitro nor the in vivo studies are definitive. There is a correlation, and there's a precedent for correlation between them that we use in many, many devices. And this is the way we do design. I mean, ideally, in rational design and evaluation of devices, you have mechanistic relationships between the in vitro and the in vivo, and you can -- and so you understand the

uncertainty better than we do, and this is our lot working in this part of the body. We cannot escape that.

So we're going to have to make judgments, and we're going to have to make judgments based upon not just the specific information we discussed in the last five minutes but all that we know about how devices work in the vagina and what behavior is like sexually and what it's like in South Africa, in terms of patterns of behavior versus what it's like, let's say, in this country. So we're going to have to make judgments.

And I, for one, would agree with Dr. Gilliam that I think the in vitro data are strong and they are informed by what we know about male condoms, in terms of the natural history of what happens in the vagina when semen is introduced.

So at the end of the day, I think we're going to have to make value judgments, recognizing that these are imperfect designs despite this, you know -- inescapably, inescapably. And I do think that the -- to me, the issue of acceptability is an intriguing one because I think what we see is a hint of greater -- of actually preference for FC2 over FC1 because it's softer and it's not as noisy. And could

that translate into a higher fidelity of usage of the device once the decision has been made to use the device.

So I think at the end of the day, we're going to have to make these value judgments regarding the meaning of the testing that's been done. And we cannot escape the fact that FC1 was approved, that it has particular labeling that is carefully circumscribed to protect the user because we're not going to be able to prove one way or another what the protection is against STIs. And so at the end of the day, we're going to have to make a value judgment with the precedent formally for our proceeding that FC1 is approved. And as Dr. Stubblefield has reminded us, we have a lot of history in terms of how we treated male condoms, and we should be informed by that.

DR. CEDARS: Dr. Thomas?

DR. THOMAS: I guess I'm somewhat confused because in going over the study --

DR. CEDARS: Can you speak into the mike a bit?

DR. THOMAS: In going over the South African study, the RHRU study, the one thing that strikes me is -- or my element of confusion comes

down to the fact that, you know, most of this data that was collected was supposedly subjective data from the patient, or from the person using the study. But now, there seems to be also this added in and taken out data that was subjective of the interviewer. There tended to be what sounds like things that were placed that were misinterpreted or -- and especially in going through this recall data, that there were elements that were put into the study, and then there were also elements that were taken out of the study.

So the question is, you know, how -- there just seems to be a lot of muddiness associated with the subjectivity of the interviewer and the interviewee coming up with what is finally purported as elements of these coital diaries.

DR. CEDARS: Someone have comments? I mean, I would think that, you know, potentially, there could be bias, but that should be true across both FC1 and FC2. And I do think that there are certain situations, as were described, where that was probably appropriate. Dr. D'Agostino?

DR. GILLIAM: May I just follow up on that point? But I think it's a mixed method study with qualitative data being used to validate quantitative

data, so rather than muddying, I think it's a triangulation and clarification of data is the way it's been presented.

And -- add to that, it's especially true when the coital log variables or assessment terms are so imprecise and imperfect for what we're trying to find out. Clearly, the coital logs are, I think, very difficult to use well in any setting, let alone when you're trying to get women to describe something that's very difficult to train them about and get them to be consistent about. It's almost impossible. So I think that you do need to combine those modes, and that probably is more of a dynamic, less precise, less objective kind of process.

DR. CEDARS: Yes?

DR. D'AGOSTINO: Yeah, I'm not sure I know what I'm being asked here. Are we being asked conceptually one doesn't have to -- given the FC1 and its history and data on that for a new contraceptive, we don't necessarily need to go through all of the procedures for pregnancy and HIV. So are we being asked a conceptual question or are we being asked if this particular study works --

DR. CEDARS: I think we're being asked a conceptual question --

DR. D'AGOSTINO: Because --

DR. CEDARS: -- of whether or not the equivalency or non-inferiority of FC2 to FC1 in terms of failure modes would in our minds be sufficient to say that this was safe and efficacious?

DR. D'AGOSTINO: Because, I mean, I think I'm comfortable saying that there's a reasonableness for this surrogate. You've sort of covered all the possible issues with the failures that you looked at. There was not the leakage taken into account, but maybe you could have something like that added to the study. I'm not sure how they could do it with the self-report. And so, conceptually, I think the idea that you don't have to run to a pregnancy study or have to have a pregnancy study for approval, given we know a lot about FC1, but I'm very uncomfortable with saying this particular study does the job.

DR. CEDARS: Dr. Warner, did you have --

DR. WARNER: I had two comments to add to that, and the first is about the need for a contraceptive study, and all the testimony in the open hearing today, it's really about STI prevention. And I realize that is, I guess, what the FDA had done with the initial device back in 1993. But I do question how relevant doing that type of study would

be in this case.

The second point I wanted to make goes back to what Dr. Gilliam said regarding the design of these trials. I just want to remind all of us that it's just as difficult to design and execute these studies for male condoms. And as a CC member, I've had to do this for the last 12 years. I was there for the NIH report back in 2000. It took a year to write that report. It's taken eight years to still sort through this evidence. So to think that the male condom literature is immune from this is not really the case.

DR. CEDARS: Dr. Gilliam, did you want to add something?

DR. GILLIAM: I had a question. I recollect that the FDA decided that some of the partial slippages were not clinically relevant, and I was just wondering how that decision was made and was it reconciled with what the company's description of a partial slippage was.

DR. WHANG: Can we bring Dr. Corrado to answer that?

DR. CEDARS: I was going to say I don't think that was the FDA that said that. I thought that was the Sponsor that said that.

DR. GILLIAM: It was in the executive summary, so I didn't know where that came from. I thought that was an FDA --

DR. CEDARS: I think that was a Sponsor comment.

DR. GILLIAM: Okay.

DR. CEDARS: If you could address that, please?

MS. BEKSINSKA: I think the issue is that the invagination has never been defined as to exactly what is part of the condom is pushed inside. It's just being pushed inside. And we tried to break it down into partial and full, as in if the inner ring -- if the outer ring is pushed inside fully or partially. We feel, and at the WHO review, it was felt that both partial and full were clinical failures. And so invagination, any point of the outer ring going inside the vagina was a risk.

In studies that have been done so far, we believe that they have also in there pushed inside included both full and partial invagination as one because the coital logs I've seen don't break it down. And so when a woman says pushed inside, the usual result is she'll say it's some or all. But what we were trying to get to, and I think it will

help uses in the future is trying to work out which of the problems is greater, the partial or the full, which will help us counsel women in the future in how to stop this failure mode.

DR. CEDARS: Dr. Whang?

DR. WHANG: Yeah, in response to Dr. D'Agostino's question about what we're looking for here, we've tried to set up the discussion questions to sort of walk through the issues that we would like your comments on. And in terms of the details of how the failure mode study was conducted or the findings of it, we'd like you to discuss those with Questions 2 and 3. So this question is really focused on this conceptual question as to whether a failure mode study is adequate for this female condom as opposed to a contraceptive or an STI study.

DR. CEDARS: And if I can summarize for you what I've taken from the discussion, and then if there are differences after I do so, please let me know. I think that the Panel acknowledges the importance and the validity of the in vitro data which, as Dr. Gilliam said and Dr. Stubblefield brought up, we perhaps have not discussed very much, that we should be informed by the male condom data and how comparator studies are done and that the FC1

was approved with careful labeling.

And so in terms of equivalency between the two, my sense is that there would be a general consensus from the Panel that that's been ascertained and that the conceptual question of does there need to be a contraceptive study, I think the answer would be no. Is that -- yes? Is that agreed?

DR. STUBBLEFIELD: I agree. I would throw in one more thing. Ultimately, we're supposed to be making risk/benefit decisions.

UNIDENTIFIED MALE SPEAKER: Right.

DR. STUBBLEFIELD: And in terms of risk of this device, there aren't any. No one has yet died from one, and the potential benefits, we've heard several. We already have the FC1 on the market. The FC2 might be a little bit better. It's not any worse. And it may increase the number of sex acts that are protected. And the main problem with all of these barriers is people don't use them. So there are a lot of reasons to think that there is significant benefit.

DR. CEDARS: Well, I think the potential risk would be if this were used instead of a male condom, which is why I think the labeling of FC1 is important to maintain.

DR. STUBBLEFIELD: Yeah.

DR. CEDARS: Because that would be the potential risk, would be the assumption that this was equivalent to a male condom, which I don't think we have data on.

DR. STUBBLEFIELD: Agreed.

DR. CEDARS: Okay. Can we move to Question 2, and, again, you have this in your packet. And this gets to some of the issues about the study design and the coital log, and we've asked a lot of questions about that. And what the FDA would like is for us to discuss the impact of these study design concerns, the dropout rate, the coital log, those issues that we've discussed to this point on data reliability and whether or not this data as presented constitutes valid scientific evidence to provide reasonable assurance of safety and effectiveness. So I'd like to open that question up for discussion. Dr. Padian?

DR. PADIAN: I had one -- so if I ask a question --

DR. CEDARS: They can come up.

DR. PADIAN: Oh, okay. So I had one lingering question -- I'm obsessed by the coital logs. And that is were there any instances where you

found a failure in a coital log but did not have it substantiated in the interview?

MS. BEKSINSKA: No, none. No, in fact, we just had -- there was one woman who broke four condoms, for instance, and one with non-clinical and three with clinical, and she was one of the few people who couldn't work out how it broke. So, in fact, some women took the condom out and they felt that there'd been some leakage, and it maybe wasn't even a breakage, but we counted it as a breakage.

DR. PADIAN: Yeah, but I just want to be sure. The specific question is, were there any instances where you counted something as a failure on a coital log where you didn't have it validated on an interview?

MS. BEKSINSKA: No. We counted --

DR. PADIAN: I'm just trying to --

MS. BEKSINSKA: I think I know what --

DR. PADIAN: I'm trying to work out the fact that the data were collected -- there was differential ascertainment depending on whether you had a coital log or not.

MS. BEKSINSKA: Yeah.

DR. PADIAN: And I'm just trying to sort out in my mind whether that would have made a

difference. So --

MS. BEKSINSKA: Okay.

DR. PADIAN: But that's helpful. Thanks.

DR. CEDARS: Other questions about -- we discussed this a fair amount with both the Sponsor and the FDA. Dr. Peterson?

DR. PETERSON: It may be the coital log, it may be other ways of getting the information with the interview, but the one thing that we've touched on a little bit but not talked about much is the -- if we look at the Table 7 and the executive summary, the real outlier relative to the other five studies is invagination, so that the FC1 is, you know, strikingly lower than most of the other studies. So the others are two to ten times greater. And now we're comparing that FC1 to the FC2.

And on the FC2, as Dr. Taylor pointed out, there's just with the point estimates, and these are statistically significant differences, the point estimate for invagination is higher for the FC2 than the FC1; just the reverse for misdirection.

MS. BEKSINSKA: Sorry, is this for the total invagination?

DR. PETERSON: Yeah.

MS. BEKSINSKA: Okay.

DR. PETERSON: Well, I'm just going from the executive summary on Table 7. So the rates for slipping and invagination -- I assume that's total ranged from --

MS. BEKSINSKA: No, I think for the invagination, it's only the complete invagination.

DR. PETERSON: Okay.

DR. CEDARS: Actually, if --

DR. PETERSON: What the FDA has said, that the comparable invagination rate is 0.52, so is that correct --

MS. BEKSINSKA: No, it's not correct.

DR. PETERSON: Okay.

MS. BEKSINSKA: The full invagination was 3 percent and 2.98.

DR. PETERSON: So, in fact, that --

MS. BEKSINSKA: Yeah, this is the complete invagination. But we've actually --

DR. PETERSON: Okay.

MS. BEKSINSKA: -- found and the WHO have stated that both partial and full invagination is the complete -- is a failure. And the other studies, when they've just put one invagination, they have also included partial. It's just that we broke it down, and I think there's been some confusion.

DR. PETERSON: Right. That'd be important to reconcile. Could the FDA help make sure we get an apples to apples comparison on that because 3 percent sounds directly in line with the other studies, and 0.5 percent is very different. So --

UNIDENTIFIED FEMALE SPEAKER: Yeah, that was what my question was, and in the executive statement on 35, it says that the FDA's review does not focus on partial invagination because they don't think it's clinically relevant. So I was asking the FDA how that choice was made, and I think that's why the tables are different.

DR. CEDARS: While the FDA is putting together the answer to that question, are there other discussion points from the Panel? Yes, Dr. Marrazzo?

DR. MARRAZZO: I have a question on the purportedly low rates of follow-up. So this design is similar to the male condom studies that have been used to prove comparativeness. Are those rates of follow-up comparable or notably low relative to the male studies that have been brought forward as evidence for comparability?

DR. CEDARS: Do people who work with the male condom have an answer to that? In other words, the dropout rate, is it comparable to a male condom

study?

DR. WARNER: Well, the dropout rate here was, what --

DR. MARRAZZO: Twenty-four percent at the first interview and 73 percent for the second.

DR. WARNER: I think that's comparable.

DR. MARRAZZO: Comparable? Okay. So the question is, I think, should we hold this study accountable to a standard that is different than what we use or has traditionally been used for male condom study comparativeness?

DR. D'AGOSTINO: What do you do with the dropout in the male condom studies?

DR. WARNER: What do we do? Well, in the --

DR. D'AGOSTINO: Just ignore it?

DR. WARNER: No, I mean, in the crossover studies, well, you take the observations from the condoms you have and evaluate those. So in the Macaluso one, for example, they crossed the male condoms for, I think, five or maybe it was ten uses, five by the female condoms, and they analyzed those condoms that they had.

UNIDENTIFIED FEMALE SPEAKER: Yeah.

UNIDENTIFIED FEMALE SPEAKER: You mean --

do you look --

DR. WARNER: I mean, in a crossover study, it's a little bit different.

DR. CEDARS: Are you asking whether you compare the people who dropped out --

DR. D'AGOSTINO: Do you impute?

DR. CEDARS: Yeah.

DR. D'AGOSTINO: I mean, most studies will, most drugs, for example, they'll ask you to impute missing data or do a sensitivity analysis to talk about what would happen if the people who dropped out were counted and they had this type of event versus that type of event?

DR. WARNER: Well, I mean, in the few crossover studies that have been done of male and female condoms, and I think Dr. Zenilman could speak to this as well with the biomarkers, I believe they just exclude those and include those events which they had collected data on. For most of the male condom studies, though, they have to look at a cohort of users and non-users and follow them over time. And you don't have that luxury with the female condom studies by the simple fact you have to recommend male condom use. And, in those cases, that's where you generally get the 80 percent I was talking about.

But those studies I think, like Dr. Peterson was saying, they're not quite the same.

UNIDENTIFIED FEMALE SPEAKER: Right.

DR. CEDARS: Dr. Stubblefield, did you have a comment?

DR. STUBBLEFIELD: Yeah, I was just thinking about the comparison of the event rates between the South Africa study and the others and that, in general, the other studies, the event rates are higher. But is it not true that the South African team that conducted this study was quite experienced with the FC1 and therefore perhaps are better able to counsel, better able to train the trainers who were training the patient? So it's not unreasonable to expect that event rates might be less.

DR. D'AGOSTINO: I mean, I thought that was one of the issues, that was one of the issues I was trying to raise, that there's a lot of counseling going on here, probably very good counseling, so can you generalize the results? What will happen when you're dealing with this and there's not the same level of counseling?

DR. STUBBLEFIELD: Well, I just say we have that problem, certainly, with all contraceptive

methods. We know that failures are higher in the first year. I suspect we have the same problem with other chronic diseases.

UNIDENTIFIED FEMALE SPEAKER: And it's true with any intervention study, any biomedical intervention study, all the HIV prevention studies.

DR. CEDARS: Well, any study where people are well cared for, the placebo group does better. So, Ms. George, did you have a comment?

MS. GEORGE: No.

DR. CEDARS: Any other discussions? Does the FDA have a response?

DR. CAREY-CORRADO: So as I understand it, the question has to do with a statement in our executive summary that reads as follows. The quote from our executive summary is:

> "The Sponsor also obtained data on non-clinical breakage, partial invagination, and partial slippage. FDA's review does not focus on these outcome measures as they are unlikely to be associated with true clinical risk, again, as they are unlikely."

And the best thing I can say about that is that our review is ongoing. As we've continued to

look at the data, look at the risk of invagination that results from an asymmetrical placement of the condom on the perineum, that now I would say at least my opinion is probably changed on that, that I do think that the partial invaginations are potentially important.

And I just want to go back to one slide that I showed. I'm sorry. I'm going to try to find it. I'm going to try to show you the slide where we talked about partial and complete invagination. That was on a per-subject basis. Let me go back on partial and complete on a per-condom basis. So I'm trying to circle around to where Dr. Beksinska just ended up, I think.

So if we looked at per-condom use, we see the number of complete displacements. Those are the acute outcomes that you actually saw in the table in the PMA that compared the two condoms. That didn't include partial. There are a whole lot more partial displacements than there are complete displacements.

The statement in the executive summary I would say I would back off on now and say that now, you know, now we've had another couple months to look at the data, to review the documents, and especially given that there is an issue with displacers, per se,

on a per-subject level, we do think that the partials are important. On a per-condom basis, the rate of displacement, if you combine the two, 3.14 on the one group, 2.98 in the other group, you know, it looks relatively benign until you get to the actual individuals and that there are individuals who tend to have a problem with displacement. And that's why we are going to focus on and include both.

DR. CEDARS: Dr. Peterson?

DR. PETERSON: Could you just go stay with this line? We've got a 3 percent total displacement and a 0.5 percent complete. And if we go back a couple of slides earlier, there were five -- six other studies that we were comparing these data to, and they range from 1 percent to --

DR. CEDARS: Five percent.

DR. PETERSON: Five percent. And are we saying now that instead of what was in the executive summary earlier, that the 0.5 is not the relevant comparison but the 3 percent is, or are those other studies that are cited there only complete, in which case the 0.5 would be the appropriate comparison group?

DR. CAREY-CORRADO: I would have to go back and look at each one of those studies to understand

better exactly what the definition of invagination was in those studies. But without going into each one individually, right now I am not prepared to say for each one what was the precise definition. But, clearly, you know, there is a spectrum of rates of this failure mode in this study compared to what is in the literature, and I think the definition of what constitutes that failure contributes to it, but it might not be the entire story.

DR. PETERSON: Yeah.

DR. CEDARS: And I think it's also important to remember that really what we're addressing in particular is this study, which, at least, whether you look at complete or partials, FC1 and FC2 were comparable.

DR. WARNER: I think we were told by our Sponsor that the answer is yes.

DR. CEDARS: And I was going to give the Sponsor an opportunity to just respond to the FDA comment --

MS. BEKSINSKA: Right. I was just going to say in all those other studies, there was only one definition, and the definition was pushed inside, invagination.

UNIDENTIFIED MALE SPEAKER: Right.

MS. BEKSINSKA: So there was no breakdown of the two. But, also, I know that people have been collecting -- from discussing this at the WHO review, people have been collecting both, but just as one. They haven't broken down. And, also, our study was done back in 2004. And in those days, the definitions were still very much evolving.

DR. CEDARS: Thank you. Dr. Peterson? Dr. Taylor, did you have something else to --

DR. TAYLOR: Yeah, I just wanted to add one other comment, which is although the failure rate, invagination rate per condom was 3 percent, if you ask a woman to use eight or ten, that translates into a 20 percent chance of ever having experienced one. So although that 20 percent number might seem high, they're using them ten times, and you're going to get that type of ever having experienced the event rate.

DR. CEDARS: Additional discussion before -- Dr. Warner?

DR. WARNER: One quick one about the sex workers, which has come up repeatedly. I just want to give -- my view is I don't see that as a problem. I think this was mentioned earlier that this is actually the exact population who you might want to be using the female condom who's not in a position to

insist on male condom use.

I think the concern that had been expressed was that commercial sex workers may have low rates of failure, but you could also make the same case for people who are married, based on the male contraceptive literature, or among people who have a lot of experience with female condoms. So there are other groups that I think CSWs are just a marker as far as experience and obtaining a low failure rate.

DR. CEDARS: So, Dr. Whang, if I can summarize the Panel's discussion for Question 2, while there were some concerns regarding data reliability, it is felt that the data are comparable to other studies in this somewhat complex area to study of contraception and that, secondly, the data should be considered sufficient.

DR. WHANG: Thank you.

DR. CEDARS: Any other discussion?

DR. D'AGOSTINO: Where did you get off with this should be sufficient.

DR. CEDARS: Well, the question is can this be -- constitute valid scientific evidence to provide reassurance. That's the second part of the question. And so if --

DR. D'AGOSTINO: I mean, I think there's a

lot of issues, and we've raised them, and I didn't know if we necessarily -- I think your summary was probably reasonable, but I -- because other studies do a bad job with dropouts doesn't mean we should continue with accepting a large dropout. If I did some quick computations, and it looks like the FC2 has a significantly higher dropout on the first phase of the study than the FC1, I think there's some issues which may mean that had they come in, the results could have gone in the other direction. I think there is a lot of issues with this study and with the data that we maybe haven't talked enough about. I think we have, but I'm not so sure your summary is capturing certainly --

DR. CEDARS: So would those concerns that you have regarding that logistical issue in terms of dropout compromise your ability to accept the data, because all we have is the data that's presented.

DR. D'AGOSTINO: Well, exactly. But I think the dropout -- I think the completeness of the question, yeah, I think there's a lot of reliability problems. We don't really know how reliable this data is. I mean, we talked about it and so forth to come up with an answer or a statement that, well, there are some problems with it, but they're all

right because it's what's in every other study. I don't -- I mean, the studies I'm involved with don't have such poor questionnaires --

DR. CEDARS: Well, the question is -- but are the studies that you're involved with studies that have to do with sexual activity?

DR. D'AGOSTINO: Yeah. I was involved all the way back with the -- in the '80s with contraceptions, and so forth, the oral contraceptions, progesterones, and so forth. I mean, I've seen a lot of those studies. I've served five or six years on the, well, what is now the OB/GYN panel. And, you know, I think we had a little higher standards in terms of asking people what they did and so forth than we see here.

DR. CEDARS: Dr. Katz?

DR. KATZ: I think we -- I just want to urge some -- I think we have to be very careful about extrapolating quantitative standards to qualitatively different types of behavioral as well as biological situations.

DR. CEDARS: Dr. Padian?

DR. PADIAN: Well, actually, one question is I don't think I really got what your point is, but that wasn't what I was --

DR. CEDARS: What's the bottom line --

DR. KATZ: Well, what I was saying is I think there are many contexts in reproduction where low dropout rates are much more easily achievable than the context within which we work today with HIV/AIDS. And clinical studies in which transmission, sexual transmission is an issue, of HIV is an issue in participation in the study.

DR. PADIAN: And what I was just going to say is I think that studies that rely on methods that are coitally dependent are I think a slightly different kettle of fish than what you were just talking about --

DR. KATZ: Right.

DR. D'AGOSTINO: Absolutely. And I'm agreeing with that.

DR. PADIAN: Yeah. I --

DR. D'AGOSTINO: Yeah, but what I'm concerned about is that somebody reading this transcript may say, hey, Lloyd, let's run a sloppy study; we already have approval, already have, you know, precedent for it. I think that what we want is just, you know, give an impression that there are better ways of getting interview data. There are better ways of chasing down the dropouts and so