FOOD AND DRUG ADMINISTRATION

REPRODUCTIVE HEALTH DRUGS ADVISORY COMMITTEE
CENTER FOR DRUG EVALUATION AND RESEARCH

New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy

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Also Present:
David A. Kessler, M.D.
Commissioner of the FDA

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P R O C E E D I N G S (9.00 a.m.)

DR. DAVIDSON: May I have your attention, please.

I would like to open this meeting of the Reproductive Health Drugs Advisory Committee, considering the topic that is well-published of this agenda.

To begin with, in terms of just some internal Committee issues, I would like to note and appreciate that this is the last meeting for three of the members who are with us today: Dr. Daling, Dr. Henderson and Dr. Zones. We certainly had the professional pleasure and benefit of their participation in this committee.

This is also the first meeting of Dr. Richard Azziz, and as has been customary, Richard, knowing that you are from the University of Alabama, I am sure you will take this opportunity to distinguish which campus that is.

Welcome to the Committee.

DR. AZZIZ: I am a professor in the Department of Obstetrics and Gynecology and the Department of Medicine at the University of Alabama at Birmingham. As we always have to say, there are three campuses, of which Birmingham is the important one.

DR. DAVIDSON: We have confirmed at the last meeting, but I would please have you note the dates of the future meetings that are at the top of the agenda today.

The conflict of interest statement will be read

today by Marina Hooten(?), who is chief of the Ethics Branch Division of Ethics and Program Integrity of the FDA.

DR. HOOTEN: Good morning.

The following announcement addresses the issue of conflict of interest with regard to the meeting, and it is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research, which have been reported by the participants, present no potential for conflict of interest at this meeting, with the following exception:

Dr. Jane Zones would like to report to reflect that she was, within the past year, a member of the Board of Directors for the National Women's Health Network, a membership-based, non-profit, public interest health advocacy organization. The National Women's Health Network is making a presentation today. However, she is not aware of what they are going to present.

Dr. Zones will be participating as a consumer representative member today, but she will not be voting with respect to this product.

In the event that the discussion involves any

other product or firm not already on the agenda for which the FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they disclose any current or previous financial interest or professional involvement with any firm whose products they may wish to comment upon.

DR. DAVIDSON: Thank you very much.

I should indicate before we begin that in addition to the Committee members seated around the table, there are four Agency persons: Dr. Phil Corfman, who is the secretariat of the Committee, who is immediately to my right; and to the end of the table to my right, Mary Pendergast, who is the Deputy Commissioner for the FDA; Dr. Kessler, who is the Commissioner and who will speak momentarily; and Dr. Lisa Rarick, who is the Acting Director of the Division of Reproductive and Urologic Drugs, a new position and a new title, for which she is to be congratulated for.

We will begin with opening comments by Dr. David Kessler, the Commissioner of the FDA.

Agenda Item: Opening Comments - David A. Kessler, M.D., Commissioner of Food and Drugs

DR. KESSLER: Thank you, Dr. Davidson. Good morning.

The purpose of this Advisory Committee Meeting is to examine the data from clinical trials of mifepristone, an antiprogestin drug, for the termination of early pregnancy. Antiprogestins work by blocking the effect of a hormone, progesterone. This hormone, progesterone, is necessary to maintain pregnancy.

Mifepristone acts by keeping progesterone from binding to its receptors, which results in the termination of pregnancy. Mifepristone is also known as RU-486 and has been available for this use in France since 1989, but was later approved in Sweden and the United Kingdom.

Since 1989, at least 150,000 women have used this drug. The U.S. rights to mifepristone were transferred in 1994 to The Population Council, a non-profit research organization. On March 18, 1996, FDA received a new drug application from The Population Council for the use of mifepristone in combination with misoprostol, an oral prostaglandin.

Their proposed regimen for the use of mifepristone for the termination of early pregnancy entails the oral administration of 600 milligrams of mifepristone

within 49 days of the beginning of the last menstrual period, followed two days later by oral administration of 400 micrograms of misoprostol.

The Agency formally accepted this application on the basis of foreign clinical data in the form of two large clinical trials conducted in France. FDA accepted this application with the understanding that the sponsor would, during the course of the Agency's review of the application, submit safety data from a recently concluded U.S. clinical trial.

The FDA classified this new drug application as a priority application because it is the first drug proposed for this indication. The goals set out in the Prescription Drug User Fee Act of 1992 is for FDA to act on priority applications within six months.

There are several parts to a new drug application. Our focus today, your focus today, is on the safety and effectiveness of this drug for the termination of early pregnancy. You will be reviewing the pharmacology, toxicology and clinical findings.

As usual, you will not be reviewing the chemistry and manufacturing controls information. Outstanding chemistry and manufacturing controls issues will be addressed by the reviewing division.

Your task today is to review the pharmacological,

toxicological and clinical data of mifepristone for its proposed indication, focusing on the science. You will hear presentations from the applicant and then you will hear from FDA's Division of Reproductive and Urologic Drug Products.

Two and a half hours have been set aside for open public hearing.

We will then seek your advice on the following questions:

Question 1: Do the results of the open-label, historically-controlled studies conducted in France establish the efficacy of this regimen for use in the United States? If not, what additional efficacy information should the applicant provide?

Question 2: The safety database for this regimen consists of trials conducted in France, preliminary data from U.S. trials and foreign postmarketing experience. Do these data adequately demonstrate that the regimen is safe for use in the United States when used for the proposed indication? If not, what additional safety information should the applicant provide?

In your discussion, we would also appreciate your commenting on the following issues:

Whether the adverse events associated with the regimen can be adequately managed when the regimen is

administered as labeled and the acceptability of the frequency of adverse events.

Question 3: Taking into consideration the overall evidence for safety and effectiveness of the regimen, do you believe the benefits outweigh the risks for the use of the regimen for the proposed indication in the United States?

Question 4: If the regimen were to be approved, do you consider the labeling proposed by the applicant on how to administer the regimen and how to monitor patients who receive it to be appropriate?

Question 5: If the regimen were to be approved, what further information, if any, do you recommend be included in the written information to be provided to the patient?

Question 6: The sponsor and the FDA review staff will discuss a proposed distribution system. If the regimen were to be approved, do you have recommendations concerning the drug distribution system proposed by the applicant?

Question 7: If the regimen were to be approved, what recommendations, if any, do you have for postmarketing studies?

Those are the questions before you today. The issue for you to consider is the safety and effectiveness

of mifepristone for the proposed indications.

To members of this advisory committee, let me simply say what I have told other advisory committees faced with making recommendations on products where there are intense feelings and differing viewpoints. What you need to do today is to focus on the science.

Let me repeat that. What you need to do today is to focus on the science. Exam the clinical data carefully. Ask the tough questions and then give the FDA your best scientific advice based on the data.

The FDA has convened this meeting to hear from the best outside scientific advisors available. The advice is not binding on the FDA, but, of course, the agency will take it very seriously.

It is important for everyone to know that as always the FDA has been very sensitive to potential conflicts of interest among its advisory committee members. Conflict of interest issues for this advisory committee meeting have been reviewed by the advisors and consultant staff of FDA Center for Drugs, by FDA's Division of Ethics and Program Integrity, in consultation with the Office of the Special Council for Ethics of the Department of Health and Human Services and by the U.S. Office of Government Ethics.

We have carefully considered the issues

surrounding any potential conflicts of interest and these potential conflicts have been resolved.

The bottom-line question for you today is whether mifepristone for its proposed indications is safe and effective.

Thank you.

DR. DAVIDSON: Thank you, Dr. Kessler.

The sponsor for this new drug application is The Population Council. The morning will be devoted to their presentation to the Committee.

I would like to indicate that though it is not noted on the agenda, at our about 11:00 a.m., we will take a 15-minute break, so that the sponsor understands that, and plan for our 15 minutes during this period from now until 1 o'clock.

The Division presentation will be the last hour between 12 and 1 o'clock.

The first presenter will be Sandra P. Arnold, Vice President for Corporate Affairs of The Population Council.

I would like that you would introduce in sequence the following presenters yourself.

Agenda Item: Presentations by the Sponsor, The Population Council

MS. ARNOLD: Thank you.

Good morning. My name is Sandra Arnold. I am Vice President of Corporate Affairs at The Population Council, as you know, the sponsor of this application.

The Population Council is, as Dr. Kessler said, an international, non-profit, research institution dedicated to exploring the causes and consequences of population growth and to improving women's and men's reproductive health.

The Council has studied mifepristone since the early 1980s and became the sponsor of this application after it became clear that doing so was the only way this drug would reach American women. Women in the United States want this drug now and there is no reason to wait.

If women in other countries, notably, France, the United Kingdom and Sweden, could have access to safe and effective early medical abortion, we felt American women ought to have this choice as well.

To make this happen, the Council immediately went to work on filing the new drug application, arranging for manufacturing and distribution and conducting clinical trials. This work has led to today's hearing.

At the International Conference on Population and Development held in Cairo in 1994, the international communities strongly affirmed that unwanted pregnancies should be prevented through expanded and improved family

planning and that unsafe abortion was a major public concern worldwide. This is also The Population Council's view.

While abortion is safe and legal in the United States, access to abortion in many communities is diminishing. Women seeking legal abortion face increasingly difficult obstacles, while abortion providers and clinic staff frequently work under potentially violent and hazardous conditions.

We support the use of mifepristone as a safe medical alternative to safe surgical abortion. Medical abortion won't replace surgical abortion, but we believe that the availability of early medical abortion eventually will improve women's access to abortion services and will make those services more private.

Women will be able to obtain medical abortion at selected doctors' offices and clinics free of violence and harassment.

The availability of mifepristone will also not lead to an increased number of abortions. It hasn't done so in France, where the drug has been available since 1989, but it will expand women's options. Medical abortion is an important option. It can be provided as soon as a woman knows she is pregnant; whereas, surgical abortion must wait until later in the pregnancy.

It avoids the use of anesthetics. It simulates a natural miscarriage and women have said that it gives them the feeling that they are in control of their own destinies. This is a safe and effective procedure, which has been used by hundreds of thousands of women outside the United States.

These are the reasons that United States women want this drug and these are the reasons that The Population Council has sponsored it.

I would now like to take a moment to introduce the people who will be presenting to you briefly.

Dr. Ann Robbins is a neuroendocrinologist at The Population Council. She has been with us for five years and she has been responsible for the mifepristone NDA.

Dr. Irvin Spitz is an endocrinologist, who has been with The Population Council for 13 years. Dr. Spitz has been involved in the clinical development of mifepristone and he designed many of the studies of pregnancy termination and other indications for this compound.

Dr. Wayne Bardin is an endocrinologist. He was Vice President of The Population Council and director of the Center for Biomedical Research for 17 years, ending in 1995, at the end of 1995. Dr. Bardin had responsibility for the oversight of this NDA preparation and he has now

turned to a career as an independent consultant.

Dr. Beverly Winikoff is a public health physician. She has been with The Population Council for 18 years. She is our program director for reproductive health. And Dr. Winikoff has had responsibility for the acceptability evaluation for mifepristone.

Finally, Dr. Elizabeth Newhall is a board certified obstetrician/gynecologist, who for the past eight years has been an abortion provider and the medical director of the Downtown Women's Center in Portland, Oregon. Dr. Newhall was a participant in the mifepristone clinical trials.

I would now like to turn the floor over to Dr. Robbins, Dr. Ann Robbins, who will provide some background on mifepristone development and on this application and will introduce the effectiveness, safety and acceptability discussions.

Thank you.

Dr. Robbins.

DR. ROBBINS: Thank you, Sandy. Good morning.

We are here today to discuss the data supporting the use of mifepristone and misoprostol for medical abortion. Today's presentations will document that this is a safe and effective method of pregnancy termination, that it is accepted and desired as an alternative to surgical

abortion by American women and that it can quite feasibly be delivered in the U.S. health care system.

If I can have the slides and the lights down, please.

I would like to begin today's presentations with a brief discussion of the key historical events that have led to the use of mifepristone and misoprostol for medical abortion, as well as to summarize The Population Council's activities in bringing this method to the United States.

This presents some of the key developmental milestones in the use of mifepristone for pregnancy termination. In 1970, the progesterone receptor was identified. Twelve years later, in 1982, was the initial report of pregnancy termination with mifepristone, demonstrated to be the first progesterone receptor antagonist.

The following year, in 1983, The Population Council filed an IND, investigational new drug application, for clinical trials of mifepristone in the United States. Following several years of testing, in 1988, marketing approval for mifepristone was granted in France and it began being used the following year.

In 1991, additional approval was obtained in the United Kingdom and the following year, in 1992, in Sweden.

This describes some of the important clinical

developments of mifepristone. As I said, the initial report of pregnancy termination occurred in 1982, following a series of testings and dose-finding studies, with the selection of a single dose of 600 milligrams of mifepristone for pregnancy termination.

How does mifepristone work to terminate a pregnancy? The next slide summarizes the key hormonal events that occur during pregnancy; fertilization, which occurs following ovulation and the luteinizing hormone surge shown here in yellow then causes an increase in progesterone secretion.

Implantation begins and takes a few days to complete and this is accompanied by a concomitant rise in human chorionic gonadotropin. Progesterone, shown here in white, is essential for the maintenance of pregnancy and mifepristone blocks the action of this hormone, as shown dramatically in the next slide.

Mifepristone, here abbreviated "mif," is given orally as a tablet. It works to block the action, to block the progesterone receptors, located here in the decidual lining of the uterus. This causes decidual breakdown, which results in a sloughing of this lining and bleeding and causes detachment of the blastocyst.

This causes a cascade of hormonal events, diagrammed here, which culminate in two important

activities, an increase in uterine contractility and cervical softening, both of which lead to expulsion of the embryo. Many women compared this process to that which occurs during a spontaneous miscarriage.

Several more years of testing showed that the addition of a prostaglandin to this regime increased the efficacy of mifepristone in terminating pregnancy. This works in the following manner. This is the same diagram I just showed you. Now, I have added the addition of a prostaglandin, abbreviated here "pg."

The thick blue line shows that the action of prostaglandin is to further increase uterine contractility. This increase in contractions leads to a greater efficacy in the expulsion of the embryo.

This regime has been tested in thousands of women. The standard regime that is used in this combination is diagrammed here. We have mifepristone delivered on visit one. Two days later on visit two, a prostaglandin is given to the women and this is followed approximately two weeks later by a follow-up visit, in which the confirmation of pregnancy occurs and, if not, the woman is given a surgical abortion.

As I have said, this has been tested and widely and shown to be a very safe and effective method for pregnancy termination. However, there was a demonstration

of very rare but serious cardiovascular effects associated with the use of one of the prostaglandins, sulprostone, which is delivered by injection.

This led to trials on alternative prostaglandins. These were several large trials conducted in France that looked at the combination of mifepristone and the orally-available prostaglandin -- orally-delivered prostaglandin, misoprostol.

The next slide shows that these studies with mifepristone and misoprostol followed the same regime I just showed you with the other prostaglandins; that is, mifepristone delivered on day one; two days later, misoprostol on the second visit. The red box here indicates the four to five hours that the remained in the clinic following the administration of misoprostol to check for any events that occur immediately after the misoprostol delivery.

And, finally, again, after about two weeks, there was a follow-up visit to confirm that pregnancy termination had occurred.

You have seen there that there is a wide variety of -- a large number of women have used this drug. I would like to now just show you some of the international experience with mifepristone. We see here that approximately 200,000 women have used mifepristone for all

purposes and the vast majority of these have occurred for the use of medical abortion.

This has been almost 190,000 of these women have used it for this purpose. You can see, 20,000 subjects have mifepristone alone; approximately 60,000 have used mifepristone plus sulprostone; 40,000 have used mifepristone plus gemeprost and an additional 70,000 have used the combination of mifepristone and misoprostol.

This is where we stand today. This drug has been tested in many, many countries and it has been approved, as I have said, in four, but not yet available in the United States.

I would like to now summarize the activities of The Population Council to register this regime within the United States. As Dr. Kessler mentioned, in 1994, in May of that year, The Population Council was granted the rights to the use of mifepristone in the United States. At that time, we began simultaneous work on two concurrent tracks of activity; first, to conduct a U.S. clinical trial and, secondly, to file a new drug application.

Of course, this is the focus of today's presentations and review, but I would like to give you some background on the U.S. clinical trial.

In the U.S., we have used the same regime that has been used in France; mifepristone given on day one, 600

milligrams. This is followed two days later by misoprostol, 400 micrograms delivered orally. Again, on visit two, the women stay in the clinic for four hours, where they are observed and then they return two weeks later for confirmation that pregnancy termination has occurred and if it hasn't, they receive a surgical abortion.

These are some of the key aspects of the clinical trial. The trial was initiated in the fall of 1994. We have enrolled 2,121 women. Women were enrolled for a gestation of up to 63 days of pregnancy, counted from the first day of their last menstrual period.

The clinical trial took place in 17 sites. These were geographically distributed across 15 states in this country and included women of all ethnic diversities. Secondly, they also were conducted in a variety of provider settings.

The enrollment was concluded last fall. We are currently in the process of finishing our data analysis of the efficacy results. However, we have included the safety results and they will be discussed later today by Dr. Bardin.

Today, I would like to emphasize right now, though, we can tell the Committee and the audience that this has been -- there have been no adverse events,

serious, unexpected adverse events, during the course of this trial and also, as you will hear later from Dr. Winikoff and Dr. Newhall, this drug is very acceptable to United States women. We will hear those presentations later.

Now, let's look at the activities that have underlined the new drug application. In the summer of 1994, we had a pre-NDA meeting with the FDA to discuss our application. NDA preparations began. The following winter of 1994, we obtained the database for the French pivotal trials.. We began audit and validation of this database and we did a full reeanalysis of the French database. These are the data that will make up the bulk of the data being presented today as they form the pivotal trial submitted in our new drug application.

In the summer of 1995 was our cutoff date for information to be included in the NDA. Throughout the fall and winter of 1995, final production of the NDA began and in the spring of this year, as you have heard, on March 14, we submitted the new drug application to the FDA.

During the summer, we submitted an additional safety update and the FDA has audited the French pivotal trial sites and the data from this trial.

For my final slide, I would like to give you some aspects of the clinical features of the new drug

application. Of course, as Dr. Kessler, our new drug application contains all the sections that you need in an NDA, but we are going to focus today on some of the clinical features.

The NDA contains efficacy and safety data on the use of mifepristone alone or mifepristone and other prostaglandins for pregnancy termination. The pivotal trials included in the NDA look at the efficacy and safety data that come from the large clinical trials of mifepristone and misoprostol that were conducted in France that I described earlier.

These two French studies enroll a total of 2,480 subjects and you will hear their safety and efficacy data presented later.

In addition, the NDA contains all of the international safety data for other clinical trials, including the U.S. clinical trial and clinical trials for uses other than abortifacients, use of mifepristone during compassionate use and data from postmarketing surveillance.

We believe the data that you will hear that are contained in the NDA prove that this is a safe and effective method of pregnancy termination.

I would like to now ask Dr. Irvin Spitz to begin the discussion of the efficacy data.

Dr. Spitz.

DR. SPITZ: Thank you. Good morning.

May we have the first slide, please.

My task this morning is to review the effectiveness of mifepristone and misoprostol for medical abortion.

Next slide, please.

This indicates the various study regimens, which have been used historically. The firstly there is mifepristone alone; secondly, there were studies with mifepristone and the prostaglandins, sulprostone or gemeprost and, thirdly, mifepristone and misoprostol. And the latter constitutes the basis of the clinical section of the NDA application.

Now, with regard to mifepristone alone, the first published study was by Herrmann and co-workers in 1982, and this showed pregnancy termination in 9 of 11 women, with duration of gestation of less than 56 days, following mifepristone administered in a dose of 200 milligram a day for four days.

Now, numerous studies have been performed since then and the results are essentially similar and these are shown in this slide; a total of 605 women, and in this slide and all subsequent slides, the number of subjects studied will be shown on the top of these bars.

So, using various dose schedules, from 140 to a

1,000 milligram, administered over one to seven days, the efficacy was 70 percent with a range of 50 to 85 percent.

Pharmacokinetic studies conducted with mifepristone showed that it was possible to use this agent as a single dose and the dose, which was, in fact, selected, was 600 milligram a day and in the total of 1,737 women, you will see that the same successful termination of pregnancy was 82 percent, ranging from 70 to 90 percent.

So, this was better than the original regimen, but, obviously, not adequate for general clinical use. So, the next main advance came with the appreciation of the actions of the prostaglandins. Now, it has been known since 1973, that uterine activity is controlled by a balance between the intrinsic inhibition of progesterone and stimulation by prostaglandins.

So, in an important study by Bygdeman & Swahn in 1985, they showed that mifepristone increases the sensitivity of the myometrium to prostaglandins. So, this set the stage for the next part of the development, the use of mifepristone and prostaglandins. Now, in the usual dose regimen, mifepristone is given on the first visit and the prostaglandin is given on visit two, which is about 36 to 48 hours after the mifepristone because this is the time of maximum sensitivity of the uterus to the prostaglandin. Then there is always a third visit after 14 days to

determine if pregnancy termination did occur.

Now, what are the types of prostaglandins which have been used? Basically, there are three types. It was first sulprostone, a PGE2 analogue, given parenterally, which requires refrigeration, is an expensive preparation and is not available in this country.

The second was gemeprost. This is a PGE1 analogue. It is given as a vaginal suppository. It also requires refrigeration, is an expensive compound and is not available in this country. Then, thirdly, we have misoprostol, a PGE1, orally-administered analogue available in 45 countries, available in the United States. It does not require refrigeration and is relatively inexpensive.

So, this was the compound, in fact, which has been used in the U.S. studies.

But, first, let us review the studies with sulprostone or gemeprost. In fact, this slide summarizes the results from the literature review in women with duration of gestation of 49 days or less with these prostaglandins. With sulprostone in over 15,000 women who have been enrolled, the success for medical abortion occurred in 95.7 percent and with gemeprost in over 2,000 women, the successful termination of pregnancy in 95.5 percent.

So, these were very acceptable results and you

can contrast it in the bottom panel with the use of mifepristone alone, where the success, as I have shown you before, was only 81 percent.

Now, the use of sulprostone was associated in approximately 1 in 20,000 women with some adverse carotid effects and this is now no longer used. The prostaglandins, which, in fact, are still used today are gemeprost and misoprostol.

As I mentioned before and you have heard from the Commissioner and from Dr. Robbins, the focus of this NDA application is mifepristone and misoprostol. This forms the basis of the two clinical studies conducted in France, which are being used to support this NDA application.

Now, what were these two critical pivotal studies? I am calling them Study 1 and Study 2. Now, Study 1 comprised women with a duration of gestation of 49 days or less and there was a slight difference in Study 2. This included women with duration of gestation of 49 days or less. But there was also another cohort of women with duration of gestation of 50 to 63 days.

So, that represents one slight difference in these two studies. In both studies, mifepristone was administered in a dose of 600 milligram on visit one and misoprostol was given in a dose of 400 microgram on visit two. And the women were then observed in the clinic for

four hours.

Now, in Study No. 2, those women, who had not had medical termination at three hours, were then given an extra dose of 200 micrograms of misoprostol, shown in the green, an extra dose, and they were observed for a further two hours in the clinic.

Then the subjects went home and there was a third visit conducted after two weeks to determine the results of pregnancy termination. So, basically, two fundamental differences; duration of gestation, 49 days and the second study 49 or second cohort, and in the Study 2, also, an additional dose if there was no medical termination of pregnancy after three hours.

So, now, I am going to review some of these aspects. I am going to now review the effect of this extra dose of misoprostol. Then I am going to review the efficacy of this regimen, considering -- and I will only review the efficacy in women with duration of gestation under 49 days, which forms the basis for this NDA application.

And subsequently, Dr. Bardin will review the safety data of all these studies, including women with duration of gestation up to 63 days. So, the first question which we have to resolve, what is the potential effect of the second dose?

Firstly, just to show you some of the numbers, total number of women enrolled, 1,286 in Study 1; 1,194 in Study 2, a total of 2,480 women who were enrolled. The number of women with gestation of 49 days or less, 1,089 in Study 1; 492 in Study 2, and a total of 1,681 women.

Then number of women with gestation of 50 days or more, there were 628, and the vast majority, as I have explained were in Study 2.

Now, let us work out the effect of this second dose of misoprostol and, in fact, this bar graph shows the outcome analysis of women, who received misoprostol with a duration of gestation of 49 days or less; again, Study 1 or Study 2.

Now, these green bars over here shows the percent, which is on the vertical axis, the percent of women, who had medical termination of pregnancy by three hours in both groups. And it was the same in both groups; 36 percent or 37 percent in both groups. So, in both groups by three hours there was a termination of pregnancy of 36 percent.

Now, these other subjects, all these other women in Group 2 were then given the second dose of misoprostol and now, let us compare the results for Study 1 and Study 2. In the turquoise, you see the number of women who had abortion after three hours and, again, in the two groups,

the results are identical. The top blue bars shows those women who had unsuccessful termination of pregnancy and the numbers are similar.

So, in fact, you will see that the results are identical, whether the women had a single dose of misoprostol or the extra dose. This is the justification. This is the justification for integrating the results together, In fact, this is shown in this slide over here.

In this total of 1,681 women with a duration of gestation of 49 days or less, there was complete medical termination of pregnancy in 95.5 percent of the women, 95.5. percent. What were the reasons for failure of medical termination of pregnancy in these 1,681 women? Well, in 1.3 percent, there was a continuing pregnancy, which was then terminated by a D&C or vacuum aspiration. In 2.9 percent, there was an incomplete abortion and in 0.3 percent, the women required dilatation and curettage or vacuum aspiration for bleeding.

What we have also attempted to do over here is to show the time of expulsion after misoprostol in these women with duration of gestation of 49 days or less. On the vertical axis, you see the percent of women with an expulsion at different time intervals; 0 to 3 hours, 3 to 4 hours, 4 to 24 hours and greater than 24 hours.

You will see that during the time of observation

in the clinic, which was from 0 to 3 and up to 4 hours, 54 percent of the women had termination of pregnancy within the time while they were in the clinic. In fact, a further 22 percent had termination of pregnancy up to 24 hours, which indicates that over three-quarters of the women had medical termination of pregnancy by -- to the end of 24 hours and only the remaining 8 percent on the data which we have had medical termination of pregnancy after 24 hours. So, this is the effect of the time of expulsion.

Now, we have also tried to determine the effect of certain patient characteristics, which could determine the efficacy results. What did we look for? We have looked at age. We have looked at height, weight. We have looked at body mass index. We have looked at gravity. We have looked at parity. We have looked at the number of previous abortions and we have also looked at the duration of gestation.

Now, it turns out that there are only two basic characteristics, which influence the efficacy of the regimen. And these are the duration of gestation and the age of the patient. Now, what about the duration of gestation? Well, the predicted probability, the predicted probability of complete medical termination in a woman of 35 days duration of pregnancy is 97 percent and in a woman with duration of gestation of 49 days, this is still high,

but it decreases to 92 percent.

So, women with a shorter duration of gestation have a better response than those with the longer duration of gestation. There is also, as I mentioned, a strong interaction between chronological age and gestational age. If one then takes women, say, at 49 days duration, a woman of 19, has a 97 percent predictive probability of complete termination of pregnancy; whereas, her counterpart at age 35, will only have a 92 percent predictive probability.

But I would like to stress that within the duration of gestation of 49 days and all the ages of all the women studied, the results were excellent with an efficacy of 95.5 percent.

Now, I would also now just like to put our results in international context and to summarize our results together with some of the other results from the literature. Again, 1,681 women with a duration of gestation of 49 days or less from the French pivotal studies, here is a literature review, all the women I could find from the literature, a total of 1,696 women. And I have compared this with the use of the other prostaglandin, the vaginal suppository, gemeprost, 2,186 women.

And you will see that with all these -- with our results, with the literature review and with gemeprost, the results are identical, complete medical termination of

pregnancy at 95.5 to 96.2 percent of the women.

Now, as I mentioned before, a formal analysis of the U.S. data has not as yet been fully completed and verification of the data collected at these sites has only just been completed now. But preliminary informal reports sent to me each week by the clinics, which have not been verified, indicates that in general the results of the U.S. study conform to the same degree to that of the international experience.

So, from this, ladies and gentlemen, I would really conclude that mifepristone plus misoprostol is effective for the medical termination of pregnancy in women with duration of gestation of 49 days or less.

So, I thank you for your attention and I will call upon Dr. Bardin, who will assess for you the efficacy data.

Dr. Bardin.

DR. DAVIDSON: The Committee may have questions.

DR. SPITZ: Certainly.

DR. HENDERSON: I actually have a question of Dr. Arnold -- I am sorry -- Dr. Robbins.

You commented several times that if the termination was not completed after the third visit, that women were given a surgical abortion. Was that an option? How did you make them have a surgical abortion? What

options were they presented at that third visit?

DR. ROBBINS: In the trials, as part of the informed consent, as part of the inclusion/exclusion criteria, that described the protocol in detail and at that time, before they signed the informed consent, they are told that if their pregnancy is not terminated by the medical abortifacient, they will need to have a surgical abortion at the end of their follow-up visit at week two.

So, they are counseled this prior to signing their informed consent and they sign the informed consent understanding that. Of course, we can never force anybody to have a surgical abortion, but all of the subjects knew that and signed their informed consent with that full knowledge.

DR. HENDERSON: What kind of risks did you give them if they were to continue the pregnancy after it had failed in medical termination?

DR. ROBBINS: This will be discussed in detail by Dr. Bardin, but I will just say briefly that they have been told that there are risks to them if they continue their pregnancy in terms of possible effects to the developing fetus. So, they were informed of this. These types of warnings are also included in our labeling and Dr. Bardin will speak to some of those when he gives his presentation on safety.

DR. HENDERSON: I assume when women came to have medical abortions in your programs, you were set up to provide them with surgical abortions. Were you ever faced, as I would imagine would happen in your life, with patients, who had no medical coverage and would have to have a surgical abortion? How do you work that into your fees?

DR. ROBBINS: You are anticipating some of the things that will come up during the presentations of the next two speakers actually. Dr. Winikoff and Dr. Newhall will talk a little bit about how this worked in the U.S. clinics.

If you don't mind, I will let them give you some of their first hand information on that.

DR. DAVIDSON: Dr. O'Sullivan?

DR. O'SULLIVAN: I have two questions.

What evidence did you present to them regarding the possibility that something would happen to their fetus? That is my first question.

My second question relates to why the final U.S. data wasn't obtained before this meeting.

DR. ROBBINS: Again, I will allow Dr. Bardin to discuss some of the information that we know about the effects to the fetus.

Go ahead, Wayne. And then I will answer the

second question.

DR. BARDIN: As part of the beginning evaluation of the drug, there is an extensive toxicology that is done on the drug, including a section called teratology.

DR. DAVIDSON: Pardon me. Is this going to be part of your formal presentation at this time?

DR. BARDIN: Not in the detail that I think it is being asked now. So, therefore, I thought it appropriate, Mr. Chairman, if you don't mind, I will answer it now.

DR. DAVIDSON: Sure.

DR. BARDIN: Because I don't have a lot of slides on it. I just was saying that there wasn't --

So, in the -- we have animal toxicology on both of the drugs. In some of the animal toxicology on both drugs, there is evidence for teratologic changes in animals. There have been 21 children born to women who changed their mind and there have been three congenital anomalies.

Now, statistically, that is not enough to determine what the effect is in humans. So, not knowing the effect in humans, we advised women about what the animal data showed and said that there was a considerable risk to them if they changed their mind because usually teratologic effects in animals will translate or have a high possibility of translating to teratologic effects in

humans.

So, these were the data that were presented to the women.

DR. O'SULLIVAN: And the three congenital anomalies?

DR. BARDIN: Beg your pardon?

DR. O'SULLIVAN: The three congenital anomalies were what?

DR. BARDIN: Three congenital anomalies in the children that were born were a club foot, some abnormal fingernails, and an immune disease which led to death.

DR. O'SULLIVAN: Long-term outcome of the remaining --

DR. BARDIN: The others are normal.

DR. O'SULLIVAN: Normal developmentally?

DR. BARDIN: We have that as of now they are normal. That is all I can tell you.

DR. O'SULLIVAN: One more question regarding toxicology. Is animal toxicology always found or always translated into human toxicology or teratology?

DR. BARDIN: Well, what you look for is a chemical reaction in the fetus that will lead to a marked abnormality of a developing organ. One has to be very concerned that if you can demonstrate this in two animal species, that this would translate into a third species.

So, I think --

DR. O'SULLIVAN: Has any primate work been done to show this?

DR. BARDIN: No. I think one does not normally do teratology studies in primates. That would be extraordinarily expensive and many people would view that to be not possible. We wouldn't get many drugs approved if that were required. So, we use two species and that is done with virtually all drugs that come before the FDA.

DR. DAVIDSON: Dr. Azziz.

DR. AZZIZ: Question for Dr. Spitz.

DR. DAVIDSON: Wait a minute. Was there a second question?

DR. O'SULLIVAN: My second question was related to why this data is being presented without the finalized U.S. data?

DR. BARDIN: If you noted the time line on Dr. Robbins' slides where she had the two arrows, the red and the blue arrows, we began everything in 1994. The U.S. clinical trial began at that time. Preparation of the NDA began with the data from the two pivotal studies. The U.S. clinical trial was completed and as you heard, the sites have just been verified and now, very soon, the analysis can begin. In other words, one has to audit all the sites, all the data, all the case report forms, verify that, lock

the data and then do the analysis.

That process is ongoing, but in the meantime running simultaneously on Dr. Robbins' two arrows, an NDA application was completed and submitted to the agency for consideration.

DR. O'SULLIVAN: I understand that. I do really understand how long it takes to collect the data and do the quality assurance, but I still don't know why this meeting is held at this time when the data is not finalized.

DR. BARDIN: Well, because we have sufficient data to -- we have two -- we have sufficient data according --

DR. O'SULLIVAN: From the non-U.S. data.

DR. BARDIN: From the non-U.S. data, to allow us to submit an application to the FDA and with the understanding that the U.S. clinical trial would be done and would be -- as soon as it was completed, the data was locked and it is all written up, it will be submitted to the FDA for their consideration.

And that is just as the Commissioner outlined. So, we are following exactly as he said.

DR. DAVIDSON: Dr. Rarick from the FDA.

DR. RARICK: I would point out to the Committee also that we have this meeting during the review process because, as Dr. Kessler noted, our goal is to take an

action on a new drug application that is submitted within six months and we would like your comments and discussion prior to that time line.

DR. DAVIDSON: Dr. Kessler.

DR. KESSLER: You should also know that FDA has insisted that not only the foreign data be presented, but the preliminary safety data that is available to date to be presented to this committee.

DR. DAVIDSON: Any further questions, Dr. O'Sullivan?

DR. O'SULLIVAN: No. I will do it later.

DR. DAVIDSON: Dr. Azziz.

DR. AZZIZ: A question for Dr. Spitz.

The regimen proposed, obviously, has two drugs. The success of mifepristone alone is 80 percent. It increases to 95 percent from the data you presented with the use of prostaglandin. How many patients need misoprostol in these studies? I mean, I assume not all of them went on to use the second drug.

DR. SPITZ: Yes, that is quite correct. The protocol called for the administration, as you mentioned, of misoprostol after 48 hours, but it turns out in this cohort of 2,480 subjects, there were 3.2 percent of women, who, in fact, had a -- whom the commission believed had a complete termination of pregnancy by the time they came to

the second visit and as a consequence, were not administered misoprostol.

DR. DAVIDSON: One question about timing.

The NDA indicates and requests the second dose at -- the misoprostol dose at 48 hours. Much of the clinical work and in your discussion, you have a window of 36 to 48 hours for that prostaglandin dose. Why isn't that specified in this application?

DR. SPITZ: In fact, basically what happens is the women get mifepristone on the first day and they come back on the third day for the misoprostol. In fact, as I did mention, the maximum sensitivity of the uterus to prostaglandins, there is certainly a window from about 36 to 48 hours. That is why we have really not specified, as long as it is specifically mentions 48 hours later on the third day they come back for the misoprostol.

DR. DAVIDSON: So, you do not advise the misoprostol being given beyond 48 hours?

DR. SPITZ: We have not studied this in detail, but, in fact, from a lot of the other reports in the literature, the best time, the best responses occur between 36 and 48 hours. After 48 hours, there is a slight fall off, not to a very great extent, but when it goes a lot beyond 48 hours, three, four, five days, then the response wears off. Correct.

DR. DAVIDSON: So, you do not advise the drug being given after 48 hours?

DR. SPITZ: No, we do not.

DR. DAVIDSON: Dr. Lewis.

DR. LEWIS: I have a question about the cardiovascular events seen with sulprostone.

DR. SPITZ: Yes.

DR. LEWIS: Did that cause any change in the qualifications of women for this protocol? Was there any predisposing factor among those women who had the cardiovascular events that led to your --

DR. SPITZ: I would just like to, you know, put on record that cardiovascular events, none have been reported with the present regimen under discussion with mifepristone and misoprostol. None have been reported and also there have been no cardiovascular reports with the other prostaglandin, gemeprost. There were only, as I mentioned, these cardiovascular effects, which occurred with sulprostone, which was given parenterally and it is believed that probably some of it got in intravenously and it is also another type of prostaglandin. And it occurs in 1 in 20,000 women. There were three cases of hypotension, one case of a myocardial infarct in the formal publication and from a review of the whole literature, there have been another two patients with myocardial infarctions, only one

of which was fatal.

So, although in the clinical studies, we have really taken cognizance really not to enroll women with -- in the pivotal studies -- the exclusion criteria really was if they had cardiovascular risk factors, they were really not included, but basically we do not believe that, in general, clinical practices would apply because no cardiovascular effects have been seen with any of these other prostaglandins, other than the parenterally-administered PGE2, sulprostone.

DR. DAVIDSON: Any other questions from the Committee?

Dr. Daling.

DR. DALING: In talking about the women, you had 21 women, who did not complete the regimen. What was the denominator for that figure? How many women were involved in that trial that resulted in 21 women changing their mind?

DR. BARDIN: The 21 women that changed their mind, they weren't all in the clinical studies. A lot of those were in general use.

DR. DALING: So, you don't have any figure on how many women changed their mind?

DR. BARDIN: In the clinical trials?

DR. SPITZ: Yes. In the French pivotal study, we

do. In these -- yes, we had -- in fact there were 13 women who never received misoprostol, 13 women. They only received the mifepristone because some of them didn't wish to have the misoprostol. They actually had termination of pregnancy. Out of this 2,480, there were 13, who did elect to go on to misoprostol.

DR. DAVIDSON: One other -- Dr. Petitti?

DR. PETITTI: In your efficacy data, you have a model, where you used various factors to predict efficacy. Was there any relationship at all, not just a statistically significant relationship between body mass index and effectiveness?

DR. SPITZ: Yes. In fact, that is an interesting question because this has been reported with the use of misoprostol, when it was given -- mifepristone alone. And, in fact, in a very careful analysis, we did not find that this body mass index had any effect whatsoever in the pivotal studies -- in these pivotal studies on the efficacy. There was some minor relationship possible with the rate of expulsion, but this was really not consistent. So, we could not find this at all.

DR. PETITTI: Was it a positive or a negative relationship, higher rates of expulsion with higher body mass index or the opposite?

DR. SPITZ: That is what it seemed to indicate.

That is correct, that the higher the weight, the earlier the expulsion, but this was really not consistently seen right through. That is why I elected not to mention it, because this is a minor -- it is of borderline significance.

DR. PETITTI: Thank you.

DR. DAVIDSON: A routine clinical use question.

In the review of your clinical data --

DR. SPITZ: If we could have that light off -- it is just very hard. I mean, I can't see anything.

Thank you.

DR. DAVIDSON: You have probably interfered with technology at a level that will not easily be excusable.

DR. SPITZ: Well, look, I gave you my qualifications.

DR. DAVIDSON: But I haven't forgotten my question.

In your clinical data -- I mean, in your research data, you excluded women with alcohol or tobacco use and also over 35. Each one of these would be practical issues in the American experience for the use of -- why were those exclusions made and what would be the advice for people who drink moderately or smoke?

DR. SPITZ: In fact, in the French pivotal -- the first pivotal French study was -- the exclusion criteria

was anyone over the age of 35. But, in fact, in the second study, there was no exclusion criteria and, in fact, 150 women were actually over the age of 35 in this. The only exclusion was if they were over the age of 35 and they smoked. This is really anecdotal. This really comes from that subject with the coronary -- with the problems with the myocardial infarction, the hypotension, where it was believed that cardiovascular risk factors might be important.

But, you know, we do not -- we have not listed that as an exclusion criteria for clinical use of this compound.

DR. DAVIDSON: Are there any further questions?

[No response.]

Okay. You may proceed with the rest of your formal presentation.

DR. BARDIN: Thank you.

My name is Dr. Bardin and I am going to review the safety of mifepristone plus misoprostol. And I think a number of the questions that have been asked will be -- maybe will move toward a better resolution as we look at these data.

I would like to begin by reviewing the rationale for reporting the adverse events for the combination of mifepristone and misoprostol, the two drugs together,

rather than separately in this presentation.

First, as you have heard, there is evidence for synergy between mifepristone and misoprostol; that is, the action of these drugs together is greater than additive. So, they are viewed then as sort of one regimen.

Secondly, women come in with lots of symptoms of pregnancy, nausea, vomiting, cramps, and then the drugs that are given increase many of these symptoms. So, we are talking about a regimen on a regimen of pregnancy.

Then, finally, there are no multicentered studies of oral misoprostol alone during a pregnancy at the dose we are recommending here.

How are these side effects or adverse events, as I am going to call them, collected? Well, at each visit, a form was filled out that in the first visit recorded the symptoms of pregnancy, in visit two, all the adverse events that had occurred since the first visit, and then there was a focus on this short four to five hour observation period after the prostaglandin, where adverse events were recorded and then there was visit three, where all the events since visit two were recorded.

Then any other emergency room visit, any other visit to the doctor for any sorts of problems, that those events were included and some patients were even followed out as long as 70 days to evaluate bleeding in women who

had had a successful abortion. All these were put together and each woman was asked to classify each adverse event as minor, moderate or severe.

Throughout this presentation, I will be referring to severe events. The two ways we think of severe events are shown on the next slide. First, there is the severe events as judged by the women themselves. These are the most common events that were seen in the clinical trial, bleeding, uterine contractions, nausea and vomiting, all predicted outcomes of the mifepristone and the misoprostol.

So, the women decided what percentage of these were severe. But we will also be referring to another kind of severe event and these are severe as judged by medical outcome. And these would be a severe cardiovascular event, any hospitalization, a surgery that was required, say, for bleeding or a blood transfusion.

I will try to distinguish which of the two kinds of severe I am talking about, as we proceed through this.

The next slide shows sort of the good news, the overview of what I am going to talk about. The animal studies show that there were no toxic effects in animals that would be reflected in the women. In humans, there were no deaths or no serious cardiovascular outcomes in any of the two pivotal studies. In humans, there were no expected adverse events. Virtually, all the adverse events

were related to the pharmacologic actions of the regimen and, indeed, some of these are essential for efficacy, such as cramping and bleeding.

The next slide shows the average number of adverse events in three different groups of women that were distinguished by the number of doses of misoprostol that they received. As you have just heard, there is a small group of subjects that have their abortion prior to the second visit. So, they receive no misoprostol. And in these individuals, shown by the red bar, they have less than one adverse event per patient.

By contrast, if you add one dose of misoprostol, the number of adverse events per patient rises to two and a second dose of misoprostol, the average adverse events per patient rises to three. As you have heard from Dr. Spitz, two doses of misoprostol do not improve efficacy. So, since there is an increase in number of adverse events in this group, we would certainly not recommend that a second dose of prostaglandin be given. And, certainly, this has been dropped from the U.S. clinical trial and it is not recommended in our labeling.

Now, what percentage of patients actually complain of one or more adverse events? Well, this is shown here with percent of patients that complain of adverse events. Here are the three groups that I have

shown you from the previous slide. So, we see that in women who receive no misoprostol, 18 percent of them complained of one or more adverse events.

By contrast, a single dose of misoprostol increases the percentage of women that complain of one or more events to 90 and a second dose of misoprostol increases the percentage to 96. Above each bar are the number of women in each of these three groups.

The blue portion of each bar represents the proportion of each group that indicated that their adverse events were severe, so that you can see that in each of the three groups, there were somewhere between 20 and 30 percent of the adverse events were judged by the women themselves to be severe.

Now, the next point is when do the majority of adverse events occur. Here we have the total adverse events shown on this ordinate on the left and on the right ordinate, we show the adverse events expressed as a percent. So that a 100 percent is equal to the total. If you look at the number of adverse events that occur immediately after the misoprostol, during the visit to the clinic in visit two, you see that 65 percent of all the adverse events that were reported were observed at that period of time.

The blue portion of each bar, as on the previous

slide, represents the proportion of the adverse events that were judged to be severe by the women themselves.

This slide puts into perspective what I have just shown you on the last slide; that is, here we have the entire time frame of observation for adverse events and there is a four to five hour period on the third day during which 65 percent of the adverse events were reported. This tells you several things, but most importantly it says that most of the adverse events were of short duration. And, in fact, except for bleeding, which can occur over several days, most events that were judged to be adverse occurred over a very short time frame.

The next slide shows you what the adverse events actually are. Here we see the percentage of women that complained of each of the adverse events that are shown here. The blue bar shows you that the most commonly recorded adverse event were painful uterine contractions occurring in 82 percent and the red bar shows you the combined GI complaints, including nausea in 45 percent, vomiting in 20 percent and diarrhea in 15 percent.

The orange bars that you can just barely see here are the next most common group of events occurring in 1 to 3 percent; headaches, 3 percent; fainting, dizziness and metrorrhagia or increased bleeding, 2 percent; anemia, asthenia and chills and fever in 1 percent.

Note here the metrorrhagia or the increased bleeding and the anemia. We will return to these when we talk a little bit more about bleeding in general. But these -- when you ask about what women think are the adverse events, these turn out to be 2 and 1 percent, even though as you will see, almost all women bleed.

Now, in order to show you the adverse events that occur below 1 percent, which I am going to do now, we have to expand this part of the scale down here so you can even see it, and that is shown on this slide, where now the top part of the scale, rather than being a hundred percent, is 1 percent. This is the incidence of adverse events with 1 percent at the top of the scale.

So you see that hot flashes occur in slightly more than half a percent, then skin conditions, anxiety, all breast conditions, including discharge, pain, itching and everything are less than half of a percent; palpitations -- this represent five subjects -- so, you see we are getting down to small groups -- tachycardia, five subjects, and toothache is out on the far end of the scale.

There were a total of 77 different kinds of adverse events reported. I have shown you 18 of those and they are the most common. So, all the rest of the adverse events occurred in something less than five patients, usually one or two subjects only.

So, I have shown you the most common adverse events, but let's now go back and look at the most common and ask how serious were they as judged by a variety of criteria.

On the next slide, we look at painful uterine contractions. For these three bars on this scale right here is percent of patients and the top of each bar is a hundred percent. So, if you look at the central bar here of above painful uterine contractions, the 100 percent here is the total women in the study. So, 82 percent of these women, shown by the green part of the bar, experience painful uterine contractions, as I have shown you from a previous slide.

Now, of this 82 percent, what portion were really judged to be severe by the women? Well, if we set that 82 percent to a hundred percent, as shown by this bar on the left and then say what are severe, then the blue portion of this bar say that 32 percent of women that had uterine contractions said they were severe.

That is one measure of how many could have been severe. Another measure would be how many needed treatment of some kind. So, if you say what percentage of 82 percent needed treatment, if you set that to a hundred percent again, as we have done on the right, and now look at that bar, 20 percent, as indicated by the yellow portion of the

bar, needed treatment.

What treatments did this 20 percent get? That is shown on this yellow bar on the far right. Now, the percentage here refers to the percentage of this 20 percent and you can see that 55 percent got antispasmodics, 31 percent, narcotics, 11 percent, non-narcotics and 3 percent all others.

People have said, okay, you have 31 percent here. Does that mean 31 percent of the women got narcotics? The answer to that is "no." It is 31 percent of 20 percent and 20 percent of 81 percent and if you quickly figure that out, that means that 5 percent of all women in the study received a narcotic for a painful uterine contraction.

So, this is the kind of analysis that we have done on each one of these to figure out what percentage of the women were actually treated and with what for their treatment.

On the next slide I will show you a similar but not so complex analysis of the GI conditions. This is the percentage of all GI conditions reported by women that might have reported one or more conditions, which would include nausea, vomiting or diarrhea.

Regardless of which one of these conditions were reported by the women, about 20 percent of women under each of these categories said that this was a severe adverse

event. However, only 4 percent of the women who had GI conditions of any type requested or received some type of medication for that event.

The next slide returns to bleeding. This reviews something that may be obvious to many of you. First, that any patient that is going to have a successful outcome with this medication is going to bleed. So, most of the women that got the medication, 96.6 bled; 33 percent bled prior to misoprostol. The mean duration of bleeding was 9.1 days and the longest duration was 69 days, with the next most lengthy, 45 days and rapidly falling off after that.

This wasn't bleeding. This was spotting and this was a women who had had a successful abortion. But it gives you an upper limit of what could occur.

Now, this doesn't tell you anything about severity. The next slide shows you severity of bleeding as judged by four separate criteria.

The first criteria, the women, while they were in the clinic, did they get any medication that could have been used to treat bleeding, saline or something that contracts the blood vessels? That kind of medication was given to 13 percent of the women. This is the upper part of the scale, this 15 percent, percent of patients who had one of these events.

Drug treatment, 13 percent. This shows the

percentage of women that had a decline in hemoglobin of greater than 20 percent by the third visit. This is 3 percent. I have already told you that 2 percent of women complained of metrorrhagia. Virtually all women bled.

The women that bled said that their bleeding in 80 percent of the time was heavier than their heaviest menstrual period, but only 2 percent of those women said that it was truly severe or excessive; therefore, we classified it as metrorrhagia or severe bleeding as judged by the individual.

1.4 percent of individuals had a bleeding event, which could be termed severe, based on medical outcome and that is shown on this slide. This is treatments for medically severe bleeding, as judged by the fact that a woman went to the hospital. That was 21 women out of 2,480. Two received a surgical intervention to stop bleeding and there were four transfusions.

Now, in the studies that you have heard about in the past, there has been great concern about cardiovascular events. So, one of the purposes of this clinical study, these two pivotal trials, was to carefully look at cardiovascular events after the prostaglandin. So, every individual that received prostaglandin had blood pressure measured and here are three measures of that examination that occurred in the clinic.

When all patients have their blood measured and you say how many patients had a decline in blood pressure of greater than 20 percent, either systolic or diastolic, it is 420. That is 17 percent of women. However, when you ask of that 17 percent how many really had what you would call clinically significant low blood pressure or clinically significant hypertension, that is only seven women in this study and only one of those was judged to be severe.

Interestingly, there was an increase in blood pressure of greater than 20 percent and almost an equal number, 16 percent, and 8 percent of women still had hypertension when they were discharged from the clinic.

Tachycardia, as I have said, was in five; one of those was severe, and even those with these who were judged to be severe, there was not a lasting serious outcome from either of these individuals.

I would now like to turn to a comparison of the severe adverse events reported to the FDA in the U.S. clinical trials, which are shown here. These are the events. These are the numbers of patients and the percentage of women out of the study that had those events and they are compared in the right hand column with similar events from the French study.

So that 1 percent of the women in both trials had

hospitalizations. Far less than 1 percent had transfusion. That is one-sixth of 1 percent and one-fifth of 1 percent in these calculations. Two percent had severe hemorrhage in both studies. Two percent of women in the United States had a surgical intervention and 1 percent in France.

So, these data look like that these studies are certainly similar.

In conclusion, the risk of adverse events has been determined in two pivotal studies. As a result, labeling has been written that informs women about the risk of this regimen.

The most frequent adverse events, painful uterine contractions and GI symptoms, were expected outcomes of the regimen. Sixty-five percent of events were immediately after the misoprostol at the time of the second visit. Eighty percent of women required no pain medication whatsoever to use this regimen.

Bleeding occurred in all women with a successful outcome. Rarely, excessive bleeding requiring hospitalization or transfusion or curettage occurred. Cardiovascular events, including clinical hypertension, hypotension and tachycardia were rare. Only two were considered severe and these were resolved without long term consequences.

So, I have reviewed for you the general data that

suggests to the clinicians and to the scientists that have evaluated these data that this drug regimen can be judged to be safe, as well as effective.

DR. DAVIDSON: Would you stay there just for one moment, please.

Dr. Rarick, would you explain to the Committee, since this word is being used often, what "pivotal" means?

DR. RARICK: I don't think "pivotal" has a regulatory definition. "Pivotal" is simply a term that is constantly thrown around as the large, well-controlled trials upon which the safety and effectiveness information is being based. The termination of "pivotal" does not have any standard definition. It is something that can be used by the sponsor or we, but it is not a regulatory defined term.

DR. DAVIDSON: Okay.

Any other questions?

DR. HENDERSON: For the treatment of symptoms, what antispasmodics were used?

DR. BARDIN: Many different ones. I can give you the list. We have them listed in the NDA, all the kinds that were used.

DR. HENDERSON: For example?

DR. BARDIN: I will have to get the list.

DR. DAVIDSON: Dr. Azziz.

DR. AZZIZ: You had a few patients, Dr. Bardin, that required surgery for excessive bleeding, most of those, I assume, are curettage, all of them. Were there other surgical interventions required?

DR. BARDIN: The surgical interventions actually defines the -- those were the -- yes, the answer to your question is those were the only kinds of surgical interventions and the surgical intervention is really how we define failure. Dr. Spitz showed the three categories of women that had a surgical intervention, those that had a continuing pregnancy, those that needed one for bleeding, which have been repeated up here, and those that were needed to remove products of conception that were not passed.

DR. AZZIZ: In your study, none of the women then required a hysterectomy for control of bleeding?

DR. BARDIN: No.

DR. DAVIDSON: Do you have any vomiting -- and even severe vomiting occurred in about 20 to 25 percent of the cases. Can you comment on whether or not vomiting occurred early enough after the misoprostol that you thought it interfered with absorption? Or can you comment about that relationship between drug effectiveness and vomiting?

DR. BARDIN: Thank you for that question. It is

very important. I am happy that you brought that up.

The way misoprostol is formulated, if you have ever touched it when your finger is wet, literally before you can get it off the end of your finger or just as soon as you can swallow it, the pill dissolves and there is very rapid absorption. Most of the symptoms arose slowly and peaked sort of around one hour and it is in accordance with the blood levels of the prostaglandin.

So, it is the prostaglandin that brings on these symptoms, as I have suggested by the slide in which almost all of the side effects occurred at the observation period and the ones that occurred by far and away the most frequently were contractions of the uterus and of the GI tract.

DR. DAVIDSON: So, in that regard, patients did not require a second dose of the prostaglandin due to --

DR. BARDIN: Almost never.

DR. PETITTI: I imagine that you have looked at your data in many ways and perhaps you have looked at this way. I would be interested in the percentage of all patients, who had at least one severe GI symptom, where the denominator is everyone who walked in the door and the numerator is severe symptom of either nausea, vomiting or diarrhea, if you have that.

DR. BARDIN: I do have that and I neglected to

make a slide of it. I don't recall it because it is --

DR. PETITTI: Perhaps you can --

DR. BARDIN: I did the same kind of analysis that I did for the painful uterine contractions, but I didn't think I could get away with showing that kind of complex slide too often.

DR. PETITTI: Well, perhaps you could --

DR. BARDIN: I will be happy to share that with you. It is written up, yes. It is actually -- it is written up in that way in the report to the FDA. So, I will share that for you. I will look it up.

DR. DAVIDSON: Dr. O'Sullivan.

DR. O'SULLIVAN: Can I just make sure I understand this. The data that you just presented is the European data. It is not the U.S. data.

DR. BARDIN: I did present the --

DR. O'SULLIVAN: The medical situation you presented was the U.S., but the side effect data of the patient --

DR. BARDIN: Yes. The patient assessment of what the patient told the doctor when they said, you know, what have you --

DR. O'SULLIVAN: That is all European.

DR. BARDIN: That is all European. That is right.

DR. O'SULLIVAN: So, we don't have any of the American as yet.

DR. BARDIN: Not yet. That will be available around the end of the year.

DR. KOSASA: What was the oldest patient that received this medication?

DR. BARDIN: Do you remember the oldest patient?

SPONSOR: 46 --

DR. BARDIN: We will look that up. We will tell you in just a minute.

DR. KOSASA: And then you don't have an indication for age on your application, so we can go up -- there is no age limit?

DR. BARDIN: No, there is not an age limit. There wasn't an age limit in the second trial and we have patients above 35 days -- 35 years. So, we have no firm date of when there should be a cutoff. We know that the prostaglandin has been used across all age groups.

DR. DAVIDSON: Dr. Henderson.

DR. HENDERSON: You obtained CBCs on all of the women who enrolled in the trial before they received the medication. Correct?

DR. BARDIN: Yes.

DR. HENDERSON: Is that part of your labeling? Are you going to suggest that all women have a CBC, a

recent CBC before they receive the medication?

DR. BARDIN: I don't think that is a requirement of the labeling. I think that every physician who cares for an individual -- the labeling says something, you should do all of the things that are required for good obstetrical practice and we focused particularly on things like RH immunizations and the precaution that one needs to take there or the precaution that one needs to take if there has been a previous endocarditis.

Then we say that any other thing that needs to be done consistent with good obstetrical practice, and, so, we didn't say get a white count, get a red count, but I think that would be included under good practice.

DR. HENDERSON: I ask only because of the incidence of anemia that you listed and if that is a concern, then might not one want to make sure that women are not anemic before they receive the medication?

DR. BARDIN: I think it is always a concern and that is -- and the percent of anemia was really judged as a fall in hemoglobin of greater than 3 grams. I think the lowest patient in the study was 10 grams, if I remember correctly. So, in many women, many women are anemic during pregnancy, but I think we will -- we are going to have a clinician, who has dealt with this talk about this, and she is going to address some of these issues of bleeding in her

presentation. And you will be interested in it, yes.

DR. DAVIDSON: Dr. Kessler.

DR. KESSLER: Dr. Bardin, you presented the serious adverse events in the U.S. clinical trial and you had a slide that compared them to the French. In your further analysis, do you believe that it is likely that those would change or is that, do you think, a relatively complete picture?

DR. BARDIN: I don't believe the transfusions will change. I think we know those. I don't believe the number of hospitalizations will change and I don't believe that any of those numbers are going to change to really make a substantial change in percentage.

DR. KESSLER: You believe that is a complete picture.

DR. BARDIN: I believe that it is certainly close. The numbers -- the number of people in those columns will change, but I do not believe that the percentages of overall women will totally change because I think there can always be a physician who didn't report something that another physician would have said was a severe hemorrhage. The physician says, oh, I see this -- I see worse than this in all the miscarriages I manage. So, they don't judge it to be serious and they don't report it to the FDA.

We will see this in our reports, but I don't think that is going to change the percentage.

DR. DAVIDSON: Yes, Dr. Narrigan.

MS. NARRIGAN: Could you just recapitulate the comparison of the American and the French data for those four events? I don't think we have that --

DR. BARDIN: If we could show the third from the last slide. So, let's see -- do you still have -- one more forward.

So, here are the serious adverse events as reported to the FDA for the U.S. trial. And here are those -- here is the number of women in the U.S. trial. Here are the number of adverse events -- the number of women who had these serious adverse events. In parentheses are their percentage of this total. And here are the same kinds of comparisons for the French data. This is the total in the French data. These are the number of women who had these adverse events and these are the percentage.

Dr. Kessler's point was to the fact that we know these numbers are absolutely with certainty and they will not change. His question was how many of these numbers do we believe might change. So, to the comparison, it is 1 percent of the patients in each trial had hospitalization. Far less than 1 percent, only 4, and in this trial it takes 24 patients -- as you can see, 24 patients, 24.8 patients

to make 1 percent. So, this is far less than 1 percent and here is 2 percent and 2 percent for severe hemorrhage or metrorrhagia, as we have called it, as it was called in the French study, and 2 percent with surgical intervention for bleeding and 1 percent in the French study.

DR. DAVIDSON: Dr. O'Sullivan.

DR. O'SULLIVAN: I do have a question.

Let's go back to surgical intervention. What exactly do you mean by "surgical interventions," before I ask my question?

DR. BARDIN: Okay. Can we turn the lights again so we can see the slide?

Okay. This is surgical intervention for bleeding. You recall, on Dr. Spitz's slide, there are three reasons for failure. A failure is when the medical abortion does not occur and a surgical procedure is required. There are three reasons for that.

Number one, if the patient comes in and they are bleeding a lot and the physician or the patient decides that is too much bleeding, a D&C is done.

Secondly, after a certain period of time it is decided that there are still products of conception in the uterus, but there is not a lot of bleeding, the surgery is not for bleeding, it is for just to remove products of conception.

Third, there is clearly a continuing pregnancy, as defined by ultrasound.

DR. O'SULLIVAN: Okay. But this is clearly for bleeding.

DR. BARDIN: This is clearly for bleeding.

DR. O'SULLIVAN: And by "surgical intervention," are you including aspiration, as well as D&C?

DR. BARDIN: Aspiration and D&C, whatever the physician used.

DR. O'SULLIVAN: It will be interesting to see how the numbers actually play out because not unexpected, in my mind anyway, is the fact that you have more interventions -- sure, it is only 1 to 2 percent, I agree, but that doesn't seem to be a big change, but there certainly is more in the U.S.

DR. BARDIN: Okay. But remember -- you have to remember that this can be either the patient or the physician.

DR. O'SULLIVAN: I understand. Yes.

DR. BARDIN: So --

DR. O'SULLIVAN: That is exactly why I am making the point.

DR. BARDIN: What you are really interested in is of the women who had interventions for bleeding, how many of them even had a change in their hematocrit, right?

DR. O'SULLIVAN: No, no. What I am really interested in is how tolerant the American woman is as contrasted to the European woman for bleeding and how much she is willing to put up with.

DR. BARDIN: That was the flip side of what I was alluding to. I would say --

DR. O'SULLIVAN: The physician's indication for doing it may be altogether different.

DR. BARDIN: We are well aware of that and that is clearly -- you are right on. That is just correct because, clearly, there are some women who said, "I have had enough; I think I will terminate this," and there are some of these and that could be because she is continuing to have bleeding which is the same as a menstrual period. That could be. But you saw that there were some women that had had a successful termination that continued to spot, and they elected not to have a surgical procedure --

DR. O'SULLIVAN: That is the European data.

DR. BARDIN: Okay, but -- well, those data will be available.

DR. DAVIDSON: Dr. Kessler?

DR. KESSLER: Can you, the best you can -- you have "hemorrhage" on this slide. You used "metrorrhagia" on a previous -- can you give us some sense generally of that definition for these data?

DR. BARDIN: In the French data, it was, as I pointed out, all women bleed, and then you ask the women what was that bleeding like and 80 to 90 percent over a series of several studies that were done in France said that my bleeding at the time I took this drug regimen was 80 -- 80 to 90 percent of them said the bleeding is heavier than my heaviest menstrual period. Okay?

So, this is a regimen that produces in most women more bleeding than their heaviest menstrual period. But then at the end of the study, all women were asked did you have excessive bleeding, and 2 percent said, yes, I had too much bleeding. That is what the 2 percent in the French study is from. It is from the women's judgment at the end of the study.

So, it allows you to kind of look at this perspective from several points of view. Women are bleeding more than their heaviest menstrual period, but only -- they have to bleed a lot before they will say it is too much.

DR. KESSLER: And the U.S. definition?

DR. BARDIN: The U.S. definition, it will be similar.

DR. DAVIDSON: Dr. Henderson.

DR. HENDERSON: In part of the material sent to us, there was a mention of someone who had meningitis. Do

you have any details on that?

DR. BARDIN: Meningitis?

DR. RARICK: There was one viral meningitis in the U.S. study.

DR. BARDIN: Oh, is that right?

DR. RARICK: A hospitalized patient.

DR. BARDIN: A hospitalized patient. Okay.

DR. RARICK: Causality has not obviously been determined. There is a couple of those.

In our presentations, we will break down some of these particular events for the U.S. If you don't have that readily available, we will.

DR. BARDIN: I don't think we have it broken down by individual patient.

DR. DAVIDSON: Are there any further questions?

DR. ROBBINS: Just to get back to some data that was asked for, so you can have it right now.

Here is the list of the different types of antispasmodics that we used for the uterine contractions. So, if you want to see that.

DR. BARDIN: It is such a long list. I am not going to -- here they are.

[Dr. Bardin hands Dr. Henderson the list.]

DR. ROBBINS: Here are some numbers in terms of the number of people in terms of nausea for vomiting and

all the severity here.

DR. BARDIN: I am going to study this and tell it to them. I am not going to try to do it up here.

DR. DAVIDSON: You want to continue with your formal presentation?

DR. BARDIN: Yes. Are we going to have a break?

DR. DAVIDSON: Will it take longer than 10 minutes? It will? Well, let's take a break for 15 minutes.

[Brief recess.]

DR. DAVIDSON: Could we reassemble, please.

Would The Population Council continue with its presentation, please.

DR. WINIKOFF: Good morning. Yeah, it's still morning? My name is Beverly Winikoff. I am from The Population Council. I am a public health physician and program director for reproductive health at The Population Council.

This morning I would like to address the issue of the acceptability of mifepristone/misoprostol for medical abortion to women and to the providers of health care for women.

Unwanted pregnancy is a serious and stressful problem for women. Safe, effective, and humane remedies for this problem have been sought since earliest human

history. Medical abortion represents a new advance in the ability to offer women options for solution of this problem.

It is important for us to know whether this is an option that women feel they would like and whether the providers of health care for women will find it a reasonable and feasible option to offer women.

Medical abortion was originally developed outside of this country, as you've heard. Since it was originally offered outside of this country, the first assessments of its acceptability to women involved patients from other countries.

The published literature shows 12 reports about the reactions of women to early medical abortion. These reports were done in six countries, all on experimental regimens, virtually all, and all on small groups of women.

Yet despite the scattered nature of this literature, the findings of these reports are consistent and strongly support a very high preference of women for medical methods of terminating pregnancy.

In general, these reports suggest the following reactions of women: medical abortion seems to be the preferred option as a choice over surgery in about 60 percent or slightly more of women in most studies.

There are very high levels of satisfaction with

medical abortion procedures recorded in all studies, and women express a great willingness to use the method again and to recommend it to others.

I would like to focus specifically now on the acceptability of mifepristone/misoprostol for early medical abortion in the United States. We are just beginning to see how American women react to this new type of therapy, and for our conclusions, we have looked to the U.S. clinical trial, interviews with patients from that trial, and focus groups of providers who participated in the trial.

We have seen through all of this information four very strong trends: one, women in the United States like this method overwhelmingly. For them and their providers, it is a very different therapy from the alternatives available to them.

Third, U.S. women seem not to differ in their reactions to this medication from women in other places. And, fourth, U.S. providers want to offer this option to women.

The first source of information that we have about the acceptability of mifepristone/misoprostol to U.S. patients come from The Population Council's U.S. clinical trial and includes almost 800 women seeking abortion who are 49 days or less since their last menstrual period.

These women were all study volunteers in the 17 participating clinics in 15 states.

Approximately one third of these women came from racial or ethnic minorities. We don't have exact numbers in these data, since the data are preliminary and may change slightly. But we have very close to clear preferences here.

The following questions were asked. These were all asked at the final visit to assess acceptability to the patients. Patients were asked if the experience was what they expected it to be, how it compared to any previous experiences they had with abortion, if they would use the method again, and if they would recommend it to others.

Half of the patients thought the experience was just what they had believed would happen. One third of the patients said that their experience was actually better than what they had thought would happen, and one in eight thought that the experience was worse than what they had anticipated.

We asked specifically about issues relating to bleeding, pain, and the place where the abortion took place. All of these issues have been cited as potentially problematic for patients, and we wanted specifically to know more about them.

With respect to bleeding, which was in almost all

cases not clinically problematic, the single most common answers were that both the length and amount of bleeding were as expected.

The next most common answers were that bleeding and pain were longer and more than had been expected. Not surprisingly, women for whom the method failed to work tended to report more and longer bleeding than women for whom the method did work.

We asked patients how painful the experience had been relative to expectations. More than half of the women reported the experience to be less painful than they had expected, and the next most common response was that the experience was as expected.

We asked women, also, if there was a problem with the time or place at which the abortion took place. Less than one in 25 patients indicated that there was any type of problem with either timing or place of abortion.

Women were asked to rate how satisfactory the entire procedure was for them overall. More than nine in ten of the women were very satisfied or satisfied with the experience, and fewer than three in 100 were unsatisfied.

Half of these unsatisfied women had experienced treatment failure. Even among the women for whom the method did not succeed overall, however, two thirds expressed that they were very satisfied or satisfied with

the procedure.

Women were asked to predict if they would choose this method again, and more than nine in ten said yes, they would choose this method of abortion again. More than three quarters of the women for whom the method did not work also said they would try the method again.

For women who could make the comparison, we asked how this method compared to their previous experience. More than nine in ten of such women rated medical abortion as more satisfactory than surgical abortion. Even two thirds of these women who had experienced failure said the medical abortion was a more satisfactory method for them.

Finally, we asked women if they would recommend this method to a friend or relative. Almost everyone in the study said yes, they would recommend this method, including more than four of five of those women for whom it did not work.

Since the United States has a diverse population, we wondered if different kinds of women would have different reactions to medical abortion. But there were no differences by race or ethnicity or method of payment in response to questions about satisfaction and reactions to other methods of medical abortion.

We plan to do more extensive analysis on these issues in the future. But we have also had a chance to

learn something about why patients may have valued the medical abortion experience so highly.

These are the reasons that emerge most commonly. Women are particularly enthusiastic about the ability to avoid surgery and anesthesia. They mention that the experience is more natural in their minds than a surgical abortion, and they value this.

Women who choose this method often comment on the sense of control or autonomy that it gives them, and they value this as compared to surgery. These themes were expressed by women interviewed in one of the clinics:

"I didn't like the idea of a surgical abortion," said one. "I don't like any type of surgery at all," said another. "I don't like anything that involves anesthesia."

Many women compare their experience with medical abortion to a miscarriage. "I've had a miscarriage before. It's just like having a miscarriage."

Some compare it to other commonly known and natural events. "It felt like my period, so it felt like a natural process."

Women clearly value the control and autonomy offered by the method. "It offers a lot more control," said one explicitly. "Your body does it itself," said another. "This was more my body discharging it than someone going in."

Patients clearly like this method, and it appears that American providers do, too. According to a survey conducted by the Kaiser Family Foundation, currently only 33 percent of all U.S. OB-GYNs provide abortion services. Yet when these providers were asked if they would provide mifepristone/misoprostol were it available, the survey predicted a 66 percent increase in the number of OB-GYNs who were offer medical abortion if it were available.

There are logistical issues with this therapy that have made some providers wonder whether they would indeed like the method. Among these issues are the fact that the counseling involved can be time-consuming; that there may need to be extra time given in speaking to patients; that providers may find it difficult to wait for the results of medical abortion when they are used to a quicker surgical procedure; that patients and providers are not used to observing the bleeding that is involved in an abortion where surgical abortion extracts the blood quickly in one procedure, but in medical abortion the blood comes out over time.

Also, some providers are worried about the logistics of serving medical and surgical abortion patients simultaneously, fearing that it could overwhelm the services that they have, and they also may fear that they need extra space and extra bathrooms, which could be

problematic.

We wanted to assess whether these issues in practice would indeed create obstacles to provider enthusiasm for the method. So we interviewed all the providers who offered medical abortion in the U.S. clinical trials. To do this we conducted focus groups in each clinic. We interviewed 78 providers of all types, including physicians and nurses and other kinds of clinicians such as midwives or nurse practitioners.

We also interviewed all of the counselors and administrators who had to deal with the drug. We interviewed people in all 17 clinics in the 15 states.

Four outstanding attitudes were apparent at all sites. One, providers want to offer this method to women, and indeed, in all the clinics, we were told that they would like to be able to offer this method on a continuing basis.

Providers think women like this method very much. Providers feel that they get better at giving this method to women with some practice. And providers become even more positive in their attitudes toward the method with some experience with it.

I want to share with you some of the things that providers said. It was clear that providers were enthusiastic about being able to offer a choice to women.

"I desperately want it here," said one doctor. "I would offer the option." "I had spent the previous 22 years working for an abortion clinic doing surgical abortions and listened to women ask, 'Isn't there some other way?'"

Providers were particularly interested in providing this method in part because they perceived it as being so well received by women. Most providers felt that women preferred medical abortion in general. Some providers said things such as, "Even the ones that failed, and even the ones that I thought had a terrible experience in terms of the physical symptoms, for the most part said, 'I would do it again. I like this method.'"

Interestingly, even with the relatively few patients that each provider was able to see during the clinical trial, the providers felt strongly that they got better at providing this method with practice. The learning curve just in dealing with this from the clinic's point of view and from the doctor's point of view. "I learned a lot," said one.

A health worker said, "We weren't very efficient at the beginning. At the end it was beautiful because we'd hardly done as well at the beginning as we did at the end."

Providers also liked the fact that they could use the women's waiting time in the clinic for counseling about pregnancy prevention in the future.

Not only did providers feel that they got better at offering the method; they also seemed to feel more comfortable with the method and actually liked it better as they gained experience with it. "I really didn't expect to like this," said one doctor. "I thought it would be very time-consuming, and I was really amazed at how easy it was and how much women liked it."

Another doctor said, "Most of us said we'd never do it. And then I realized, no, I'd take mifepristone. I'd rather do it instead of taking my chances with who knows who out there for a surgical procedure."

These first experiences with mifepristone/misoprostol suggest that it will be well received and well managed by American physicians. We need to realize, however, as we go forward that the system of distribution of this drug in Europe, where it's now used, is quite different from our usual distribution mechanism for pharmaceuticals in the United States.

As a result, we intend to begin distribution of this drug quite cautiously in a mode similar to the way that international experience with this drug has occurred so far.

Because this therapy will be new for American physicians, there will be extensive provider education in how to provide this treatment to patients.

Mifepristone will be supplied directly to providers by the distributors, and it will not be sold in pharmacies. It will be provided to physicians who have training in the dating of pregnancy, the diagnosis of ectopic pregnancy and surgical abortion, and who have access to facilities for surgical abortion and for emergency treatment of complications in order to make sure that physicians can provide this drug in the future as safely as it has been provided in the clinical trial and as safely as it is being provided elsewhere.

The administration of the drug will also be subject to some limitations. Stocks of the drug will need to be kept in a secure location. Providers will have to keep a record of each dose administered, and patient information will be included in each package of the drug.

The administration of the medication will be on site and under supervision of the physician. There will be also extensive informed consent documents in each package.

In conclusion, regarding acceptability and feasibility of this method, mifepristone/misoprostol for early medical abortion is a safe, effective, and highly acceptable therapy; U.S. physicians will offer it, thereby increasing access to services; and women will have a new choice that will make abortions earlier and therefore safer for them.

Thank you very much.

DR. DAVIDSON: Are there any questions? Dr. Azziz?

DR. AZZIZ: In regards to your data concerning the satisfaction of women who actually failed therapy, how do you potentially measure that in regards to the reliability of your data? One would assume that most women who failed the therapy would probably not be very satisfied with the therapy as a whole. Yet about half of your women who failed appear to be satisfied. Does that in any way question the reliability of the positive data?

DR. WINIKOFF: I don't think so. I think women were rating an overall experience with a clinical situation, and they were treated with respect and given a lot of information and tried the best they could to avoid surgery, and when they couldn't avoid it, they had it and they felt they had been given a fair shake. So I think they were satisfied with their experience. It was an experiential question.

DR. DAVIDSON: Dr. Zones?

DR. ZONES: As I recall in the protocol, women had to live or work within an hour of the provider's site?

DR. WINIKOFF: Yes.

DR. ZONES: That may be in the French studies.

DR. WINIKOFF: I think it was work -- within an hour of work or home, a place where they could get emergency treatment.

DR. ZONES: Right. Do you think that's adequate, and do you think that should be on the label?

DR. WINIKOFF: As we've said before, this drug essentially induces a miscarriage. If women can have miscarriages in any given place with safety, they can have medical abortion. The U.S. health care system is adequate to deal with the kinds of emergencies that we have seen in this trial and that the French have seen. I think that that's more than adequate.

DR. DAVIDSON: Dr. Henderson? Or Dr. Kosasa?

DR. KOSASA: I just wondered, is it available in pharmacies in Europe right now?

DR. WINIKOFF: To my knowledge, not. To my knowledge, it is distributed directly to the clinics that provide it.

DR. HENDERSON: I actually have a couple of questions. The first, at the beginning of your presentation, you said that 60 percent of the patients actually preferred the medical termination of pregnancy. Was this the general population or was this the population who had already had a medical and a surgical termination?

DR. WINIKOFF: This is a meta-analysis of studies

that were done in other countries in which women were offered a choice.

DR. HENDERSON: Had they had a termination?

DR. WINIKOFF: No, this is the whole population. It's all takers. This is just a generic -- it's all takers, and the actual range is pretty much 60 to 70 percent.

DR. HENDERSON: Okay. You mentioned that during the time that women waited to bleed or their bleeding was observed by the providers, they had contraceptive counseling. Do you have any indication of how effective that was, how many women before they had this medical termination used contraception and if that changed after they had the procedure?

DR. WINIKOFF: We will be able to look at some of those issues more clearly from the individual patient data when the data are available to us. Now I have the focus groups from the providers, who said that the providers thought it was a good experience and that they were able to give more information to women. But we don't have the patient data on that yet.

DR. HENDERSON: Okay. And you mentioned that -- all the things that have to be required in order to have a practitioner use it. It seems to me that you're pretty much excluding family practitioners and other primary care

providers who are not OB-GYNs. Is that not a market that would need to be addressed, and if people have to be able to do all these things that family practitioners and pediatricians may not be able to do, how do you get them access to OB-GYNs, essentially?

DR. WINIKOFF: I'm not an OB-GYN, and I can do all those things. Most American physicians are trained to do all those things.

DR. HENDERSON: Doing surgical suction?

DR. WINIKOFF: Training in surgical -- it doesn't mean they currently do it.

DR. HENDERSON: Suction in termination?

DR. WINIKOFF: Training, because D&C, after all, most medical students know how to do that.

DR. HENDERSON: Mmm, okay.

The last thing --

DR. WINIKOFF: Not necessarily for abortion, but the surgical procedure is the same.

DR. HENDERSON: The other thing is, you want physicians to essentially manage the pharmaceutical, and how -- if that's going to be your primary mode of distribution, I wonder how you're going to train physicians who are just now dealing with managing medical records more accurately and appropriately, to now have them held accountable for managing pharmaceutical drugs that have to

be recorded and accounted for.

DR. WINIKOFF: Actually, this is very parallel to how the IUD is provided, and physicians do that. Physicians now manage narcotics which actually have legal restrictions on them that are more stringent. So I don't see why it should be a problem. But, obviously, it is something that one has to consider as one goes, and if there are problems, we would have to solve them. But I don't anticipate that that would be a problem.

DR. DAVIDSON: Are you finished?

DR. WINIKOFF: I understand in Europe it was distributed that way. Why have you consciously elected to eliminate the pharmacy as a means of controlling and distributing it to a variety of people and not just people who seek out a distributor?

DR. WINIKOFF: Do you mean the pharmacy on the street or the pharmacy in a hospital?

DR. HENDERSON: Any pharmacy. The pharmacy system that we have in the states.

DR. WINIKOFF: Well, it seems to me more efficient to control the distribution through the provider who has to provide it, because if it is in a pharmacy, then the woman would go get a prescription and bring it back. It didn't make kind of logistic sense. But this is not to say that these guidelines -- these are guidelines that we

think are wise to start with. It doesn't mean to say that with greater experience in the American context, we can't have a more tailored distribution system as it evolves. Certainly we don't intend for any of the usage to be set in stone. As the scientific data are not set in stone and as more information becomes available, all kinds of things can be inserted into the information and changed.

DR. DAVIDSON: Dr. Kessler?

DR. KESSLER: Several questions, Mr. Chairman.

In your proposed labeling the agency has received, you have that the patient must be able to reach emergency medical facilities equipped to provide surgical termination of pregnancy, blood transfusions, and emergency resuscitation if necessary within one hour of home or work during the treatment procedure until discharged by her physician.

Did I understand you to say that that was not any longer going to be a requirement, or is that in fact a requirement?

DR. WINIKOFF: As I understand it, everything that you have in the labeling still stands.

DR. KESSLER: So that requirement stands.

The second question. In just looking at, in your presentation, on the focus groups -- I assume that is in the interviews -- you list a lot of positive comments about

control, natural, avoidance of surgery. Those were your headings.

DR. WINIKOFF: The patient.

DR. KESSLER: Those were the patient comments. Can you give us a sense of the negative statements, if any, that you have received?

DR. WINIKOFF: Some people commented on the amount of blood they saw, that they hadn't expected -- the ones who saw more blood than they expected. Some people commented on the length of staying afterwards, after the misoprostol. They didn't feel they needed to stay that long, and they felt that was an encumbrance.

Some people wished they could have taken it at home. There, I mean, that was sort of the general range. Some people commented on whatever side effects they may have experienced that they didn't like. Basically, there were a lot of positive comments and not as many negative comments, I have to say.

DR. DAVIDSON: What about the time and inconvenience of these multiple visits?

DR. WINIKOFF: Yeah, the time was commented upon in a couple of ways. The length of the second visit was the main obstacle. The second -- people didn't -- I mean, this is a self-selected group. It was offered the method knowing that they would have to come. So for the people

who were offered the method, that wasn't such a big problem, but after experiencing the waiting in the clinic, some people felt that it was too long.

DR. DAVIDSON: Did you have any --

DR. KESSLER: One last question. If you look at -- going back to Dr. Bardin's slide on the serious adverse events both in the French trials and the U.S. trial, if you look at hospitalizations or transfusions, is there any way when you look at those to suggest how they could be prevented, how any of these -- does the distribution scheme help prevent any of those serious adverse events?

DR. WINIKOFF: I think counseling women on the amount of bleeding and helping them to assess when they should come back is very important. The more we learn about this drug, probably the better we'll be able to communicate with women about those issues.

People need to come back to the providers who provide the method so that people are familiar with when to advise them to have a surgical termination or when they need further treatment and when they can wait, and as we said, as people gain experience with the method, it becomes very important that these issues, as you'll hear from Dr. Newhall, are very striking to the providers of the method.

So we need to communicate these issues about what

to expect to the patients so that they know how to manage the situation in conjunction with the providers.

DR. DALING: I have one question.

DR. DAVIDSON: Dr. Daling?

DR. DALING: Did 100 percent of the patients come back for the second and the third visit?

DR. WINIKOFF: Yes.

DR. DALING: Amazing.

DR. DAVIDSON: Dr. Azziz?

DR. AZZIZ: Dr. Winikoff, just to come back to the comment that Dr. Henderson brought up in regards to the use by physicians who are not surgeons -- and I disagree strongly; there is no training in D&Cs other than surgical specialties. But in your recommended labeling, it simply states that patients should live within an hour of a surgical facility that does not have to be the same facility that they had the medications.

DR. WINIKOFF: Right.

DR. AZZIZ: Is that correct?

DR. WINIKOFF: That's correct.

DR. AZZIZ: So there is no exclusion of family practitioners and internal medicine? There was that impression when you responded earlier.

DR. WINIKOFF: No, no, I didn't mean to. It was the question that implied that. I certainly didn't mean to

respond that way. We feel people need to know when a person needs surgical intervention and to be able to get it. We don't mean to imply that people all have to be able or be ongoing providers of surgical methods.

DR. AZZIZ: Thank you.

DR. DAVIDSON: Yes, Dr. Narrigan?

DR. NARRIGAN: I just have a question about the 800 people in your sample. Did that include any of the women who had adverse effects that were in the table of severe adverse --

DR. WINIKOFF: Yes.

DR. NARRIGAN: It did?

DR. WINIKOFF: It includes all the women equal to or under 49 days LMP for which this approval is being sought in the American study.

DR. NARRIGAN: I thought the American study was 2,121.

DR. WINIKOFF: Yes. Yes, but this is all the women -- that study goes to 63 days. So this is all the women -- it's a subset of the women within that study, the women who had 49 days or less LMP from that 2,121, which is about 800, 797 to be exact.

DR. NARRIGAN: Okay, thanks.

DR. DAVIDSON: Any further questions? Dr. Zones?

DR. ZONES: You mentioned that there was no

difference between racial and ethnic groups on satisfaction?

DR. WINIKOFF: Yes.

DR. ZONES: This may be jumping the gun, but were differences found in these various social status-type groups on other variables?

DR. WINIKOFF: I only looked at the acceptability data. That's all that was available to me now. We'll have to look at the other things later. But with regard to all these acceptability questions, there were no differences found.

DR. DAVIDSON: Any further questions? Dr. Henderson?

DR. HENDERSON: Before we're done, is there any plan to give us demographics on the 2,121 patients who were in the States, the racial, the smoking histories, or the method of payment of any of these women? Just the demographics. I understand that you don't have the results, but --

DR. WINIKOFF: It's about a third, as I mentioned, DR. HENDERSON: Right. You said --

DR. WINIKOFF: Other than Caucasian, as recorded as other than Caucasian.

DR. HENDERSON: Right, but Asian, African-Americans --

DR. WINIKOFF: That third is split, and I have the data. I can -- but it is all preliminary data and we --

DR. HENDERSON: And method of payment or any smoking history?

DR. WINIKOFF: Smoking history I don't have. The method of payment is -- it's method of usual payment for medical care, and many people had multiple answers. So it's going to be hard to disaggregate that data well. We'll have to look at it a little bit better.

DR. DAVIDSON: In the world of acronyms and few syllables, these two drugs are quite a repetitive mouthful.

[Laughter.]

I wonder, have you some abbreviated means of referring to this?

DR. WINIKOFF: No.

[Laughter.]

DR. DAVIDSON: Your answer is --

DR. WINIKOFF: My answer is no. We would love it. But the ones that we've come up with or that other people have tried out haven't worked for various reasons. But we look forward to having an actual trade name at some point that will be simpler.

DR. DAVIDSON: Okay.

DR. WINIKOFF: But you saw Dr. Robbins' slide had

M-I-F. Some people say "mif" sometimes.

DR. DAVIDSON: Okay. Thank you very much. I will not lean to my temptation.

[Laughter.]

Okay, could you continue your formal presentation?

DR. WINIKOFF: Sure, thank you. I would like to introduce to the panel Dr. Elizabeth Newhall from Oregon. Dr. Newhall is one of the investigators of the clinical trial, and she will discuss her experience with this regimen.

DR. NEWHALL: Good morning. And yes, we did call it M&M.

[Laughter.]

I'm happy to have the opportunity to share with you my experiences with mifepristone in Oregon.

I am a board-certified obstetrician-gynecologist. I am a 1979 graduate of the University of California at Davis, and I began my career as an emergency room physician prior to turning to gynecology in 1984. I served on the faculty at Oregon Health Sciences University before beginning my private practice in 1990.

Concurrently, for the past eight years, I have been a provider of abortion services and the medical director of the Downtown Women's Center, where we conducted

the Oregon portion of the mifepristone trials.

Beginning as a premed birth control counselor in the early 1970s, I have been a participant in women's health care for 23 years.

My experience with mifepristone is solely as an abortifacient. However, like my colleagues, I am excited about its other clinical uses in gynecology.

Simply put, mifepristone is an effective, safe, well-tolerated medical abortifacient. Moreover, American women very much want the option of medical abortion available to them. Already familiar with the monthly process of uterine emptying, women who choose mifepristone perceive the process as more natural and much less scary than a surgical procedure which in no way aligns so closely with their endogenous physiology.

Clinically, a mifepristone-induced abortion is identical to a spontaneous miscarriage, except that it is quicker. Biochemically, it is not dissimilar, in that placental support is withdrawn and then the misoprostol engages the sensitized uterus in expelling the products of conception.

We conducted our trials at the Downtown Women's Center, which is on the ninth floor of a downtown office building in Portland. We serve women of broad ethnic variety there. Women began calling for this option as soon

as RU-486 was in the news and in huge numbers as soon as it became known it would be available in Oregon.

They still call regularly, even though the studies have been over for a year, because so many women seek the option of early pregnancy termination.

Women who met the screening parameters presented on Monday afternoons for counseling, consent, dating, ultrasound examination, and then met privately with the physicians for examination and discussion.

Following this, they took the mifepristone and went home. On Wednesday mornings, they returned for the misoprostol dosing, where, in our erstwhile recovery room, we had folding cots set up in two facing rows, sort of M*A*S*H style, where anywhere from six to twelve women began their expulsions together.

I had predicted that women would reject the notion of having an abortion as a group experience. However, it turned out to be completely the opposite. There was a lot of group support, a lot of camaraderie, and a lot of conversation between the women really helping themselves through this process, and the group turned out to be (an) unanticipated advantage to the method.

The usual experience was, about an hour or two after taking the misoprostol, sometimes immediately, cramping and bleeding began, both a bit more intense than a

regular menstrual period. This lasted about one to two hours. Both let up noticeably. With a somehow distinct episode of bleeding, almost all the women knew when their expulsions were complete, although none were able to discern any difference between the blood -- or see any tissue. They all just saw blood and blood clots.

The women read books, they played cards, they talked about politics, they laid quietly and looked out the window at downtown Portland. Some were sad, some were pensive. They drank tea and made frequent trips to the two bathrooms, which, incredibly enough, were adequate for all the women.

Less than half the women took a pain pill or two and very rarely -- you know, maybe every three weeks or so -- there was a woman who was so uncomfortable that she required an injection for either pain or nausea.

The difference in an afternoon spent in surgical abortion as opposed to an afternoon or morning spent in medical abortion was really very noticeable in the amount of adrenaline generated both among the patients and the staff who cared for these women.

After completion of the expulsion and ultrasound documentation, many women just had to sit around and wait for the four-hour observation time to pass. I can remember only one woman who remained after the four-hour time period

because she was so uncomfortable, and we ended up doing a suction on her by the end of the day simply to end her cramping, not because of any bleeding or medical necessity.

The nurses who tended these women, while completely capable of handling all aspects of surgical abortion independently, had rarely if ever witnessed the amount of bleeding that attends a spontaneous miscarriage or even a heavy menstrual flow.

In the surgical abortion setting, that amount of bleeding is not long tolerated. And so, initially, it was hard for them to stand by and watch, much less be reassuring, as they knew that their standard process would end it in about a minute.

The learning curve was very rapid, however, and the flow dropped very quickly to a more familiar level. They relaxed and were educated.

Those of us with wider experience in reproductive medicine who deal regularly with births, miscarriages, spontaneous loss and even fibroids were much more comfortable from the beginning.

Physicians who already work in these areas will have much less of a learning curve in this sense. They know that women regularly bleed heavily for short periods and almost never incur significant anemia or other ill effects.

Our average drop in hemoglobin was slight to minimal. We always check hematocrits prior to an abortion of any kind, but we never deny abortion to women with anemia because birth poses a much greater risk of blood loss.

Any facility or physician that currently provides care to women having miscarriages is quite adequately prepared to handle women undergoing medical abortion. The women themselves were generally quite comfortable with the amount of bleeding, needing at most reassurance that it was as expected.

We had no infections, we had no uterine damage, we had no ectopic pregnancies, and we had no transfusions.

There were a few women who became intolerant of the sometimes prolonged light bleeding. Abortion providers again are facile with the ultrasound at detecting even small amounts of uterine debris and are used to offering women with surgical abortions resuctions for the same symptoms following a surgical abortion, where again no bleeding is what we prefer.

Because of the political atmosphere being so scrutinizing around abortion medicine and because everyone is very interested in having satisfied patients, women are very coddled in our clinic and are encouraged to participate fully in their decisions and are given all

options at all times about anything that they want.

This and the safety and success of our surgical approach made us more quick, I am sure, than our European colleagues to offer suction for provider and patient convenience rather than out of overt medical necessity, especially since, in Europe, most D&Cs are done under general anesthesia, whereas here, at least in our clinic, the vast majority are done with the patient awake. I am certain, as our experience grows, the number of suctions will lessen.

The women who did come to surgical intervention despite having preferred initially to avoid it were very accepting when it became obviously the right thing to do. Accepting surgery as an indicated backup procedure was much more palatable than choosing it as a primary procedure. No women refused, and most did not have an ongoing pregnancy.

Which brings us to why women want mifepristone and, indeed, the option of medical abortion in general. While mifepristone has been delayed, more and more women are calling, seeking and obtaining medical abortions with an alternative drug which is much less preferable than mifepristone.

The reasons women have for choosing medical abortions are as varied as women are. Some reasons are conscious, some not. They include a general fear of