In Europe, over 52,000 women have received mifepristone followed 48 hours later by misoprostol without serious heart complications.

2. SUMMARY OF STUDY

The aim of the study is to determine the safety, efficacy, acceptability and feasibility of mifepristone plus misoprostol in inducing abortion, within the U.S. health care system setting, when administered to women exhibiting amenorrhea of varying duration (up to 63 days). **The duration of amenorrhea will be defined throughout this document as the number of days from the first day of the last menstrual period.** In addition to the large pivotal studies, a small initial pilot study will be conducted to enable the investigators to gain first hand experience with the proposed dosing regimen.

A total of 1,050 pregnant subjects will be enrolled in this and an identical sister protocol, to be conducted simultaneously. Thus a total of 2,100 subjects will be enrolled in the two trials. Three groups of subjects will be examined:

Group 1: Amenorrhea of $\leq$ 49 days
Group 2: Amenorrhea of 50 through 56 days
Group 3: Amenorrhea of 57 through 63 days

Analysis will also be conducted on safety, efficacy and acceptability of all subjects taken as a single group, regardless of the duration of amenorrhea. This will be a multicenter trial utilizing a minimum of six centers in each of the two studies. The centers will all perform pregnancy interruption on a regular basis. The centers will have access to facilities for blood transfusion and routine emergency resuscitation techniques. In all the trial centers, the recruitment of subjects will be such that, as closely as possible, equal numbers of subjects will be enrolled into each of the three groups defined above.

Subjects shall visit the study center three times, unless state law requires an additional, initial informational visit with a mandatory waiting period before the process can begin. At the initial visit (Day 1; after any required statutory waiting period), a full history and physical examination will be performed and the duration of amenorrhea will be determined and the reasons for selecting a medical abortion will all be recorded. At this visit, 600 mg of mifepristone (three 200 mg tablets) will be administered. The subject will return to the study center for the second visit on Day 3 to receive oral misoprostol (400 μg as two 200 μg tablets). The subject will be monitored at the center for at least four hours post the administration of the prostaglandin. The third visit will occur on Day 15. At this visit the completeness of the medical pregnancy termination will be assessed. In the event that the pregnancy is on-going at this time, or if the abortion has been incomplete, either vacuum aspiration or dilation and curettage will be performed. Subjects who undergo a surgical abortion at any time during their enrollment in the study

will return to the center two weeks post the surgical procedure for a follow-up assessment.

3. OBJECTIVE

The objective of this trial is to evaluate the effectiveness, safety, acceptability and feasibility of mifepristone plus misoprostol in inducing abortion when given to women, who have experienced up to 63 days of amenorrhea, within the U.S. health care system setting. Prior to initiation of the pivotal studies, a pilot study comprising 15 women will be performed at each of the selected study centers. The purpose of this pilot trial is to give the investigators exposure to the proposed dosing regimen so they will have first hand experience prior to the initiation of the pivotal studies. The results of the pilot trial will be included in the safety analysis for the product, but the efficacy data will be treated as a subgroup analysis relative to the pivotal trials.

Investigators selected to conduct the trials will be experienced abortion providers and medical investigators. They should have access to an IRB able to review the protocol, and will have malpractice insurance as well as general liability insurance for the clinic, hospital or office where the study will be performed. The investigators should be able to complete the study in six months at a maximum.

The investigators will operate in an appropriate study center; the study center will:

a) Provide routine emergency resuscitation such as O_2, Ambu bag and will be staffed with personnel trained in routine emergency care.

b) Have access on a 24 hour a day basis to blood transfusion, D & C and more elaborate resuscitation procedures.

c) Have space to conduct the study including a room where a woman can be monitored for at least four hours after the prostaglandin administration.

d) Have the physician responsible for the study on call on a 24 hour a day basis, or his/her delegate of equal qualification.

e) Have adequate and sufficient trained personnel for counselling of subjects and conduct of the study.

f) Have transvaginal ultrasound available and personnel trained in the use of the equipment as well as the interpretation of the sonograms for the assessment of gestational age in relation to the reported duration of amenorrhea.

g) Investigators and staff will answer a provided questionnaire at the completion of the study.

4. PATIENT SELECTION

4.1 Patient Sample:

4.1.1 Number of patients: A total of 1,050 patients per each of the identical trials for a total of 2,100 subjects will be enrolled at multiple centers.

4.1.2 Age range: 18 years or older.

4.1.3 Residents of the United States.

4.2 Inclusion Criteria:

4.2.1 Good general health.

4.2.2 Age 18 years or older.

4.2.3 Request termination of pregnancy.

4.2.4 Agree to undergo surgical pregnancy termination in case of failure of the medical abortion method being evaluated.

4.2.5 Have an intrauterine pregnancy of known duration which is less than or equal to 63 days of amenorrhea period. The final determined estimated duration of pregnancy should be less than 64 days of amenorrhea, and as confirmed by uterine size on pelvic examination and ultrasonographic examination.

4.2.6 Have a positive urine pregnancy test.

4.2.7 Willing and able to participate in the study after its precise nature and duration have been explained.

4.2.8 Able and willing to sign an informed consent form.

4.2.9 Resident of the United States.

4.3 Exclusion Criteria:

4.3.1 Evidence of the presence of any disorder which represents a contraindication to the use of mifepristone (e.g., chronic corticosteroid administration, adrenal disease) or misoprostol (e.g., asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or known allergy to prostaglandin).

4.3.2 History of severe liver, respiratory, or renal disease or thromboembolism.

4.3.3 Cardiovascular disease (e.g., angina, valve disease, arrythmia, cardiac failure).

4.3.4 Hypertension being treated on a chronic basis or untreated patients who present with: a blood pressure of > 140 (systolic) or > 90 (diastolic).

4.3.5 Anemia (hemoglobin level below 10 g/dL or hematocrit below 30%) at the Day 1 visit.

4.3.6 A known clotting defect or receiving anticoagulants.

4.3.7 Subjects with an IUD in place.

4.3.8 Insulin dependent diabetes mellitus.

4.3.9 More than 63 days of amenorrhea or results of bimanual pelvic examination or vaginal ultrasound which are inconsistent with 63 days or less of amenorrhea.

4.3.10 Breast-feeding.

4.3.11 Adnexal masses or adnexal tenderness on pelvic examination suggesting pelvic inflammatory disease.

4.3.12 Ectopic pregnancy or threatened abortion.

4.3.13 Women 35 years of age or older who smoke more than 10 cigarettes per day and have another risk factor for cardiovascular disease (e.g., diabetes mellitus, hyperlipidemia, hypertension or family history of ischemic heart diseases).

4.3.14 Unlikely to understand or comply with the protocol requirements.

4.3.15 Women who cannot reach the source of emergency medical care that serves the abortion center within one (1) hour from (a) their home or place of work and (b) the abortion center.

5. STUDY MEDICATION

5.1 Assignment of Study Medication

This is a multicenter trial evaluating the effectiveness, safety and acceptability of mifepristone plus misoprostol in inducing abortion when given to women in one of three groups depending upon the duration of amenorrhea. The three groups are:

Group 1 - Amenorrhea of $\leq$ 49 days
Group 2 - Amenorrhea of 50 through 56 days
Group 3 - Amenorrhea of 57 through 63 days

As closely as is possible, equal numbers of subjects will be enrolled into each of the three groups. There may be differing numbers of patients enrolled from center to center, but the number per group per center should be approximately one third into each of the groups.

5.2 Dosage and Administration

There will be three visits to the study center. At the initial visit (Day 1), a full history and physical examination will be performed and the duration of amenorrhea will be determined and the reasons for selecting a medical abortion will all be recorded. At this visit, 600 mg of mifepristone (three 200 mg tablets) will be administered orally. The subject will return to the study center for the second visit on Day 3 to receive oral misoprostol (400 μg as two 200 μg tablets). The subject will be monitored at the center for at least four hours post the administration of the prostaglandin. The third visit will occur on Day 15. At this visit the completeness of the medical pregnancy termination will be assessed and an acceptability questionnaire administered. In the event that the pregnancy is on-going at this time, or if the abortion has been incomplete, either vacuum aspiration or dilation and curettage will be performed. Subjects who undergo a surgical abortion at any time during their enrollment in the study will return to the center two weeks post the surgical procedure for a follow-up assessment.

5.3 Packaging

A) Mifepristone — Mifepristone will be provided as 200 mg tablets of micronized mifepristone.

B) Misoprostol — Misoprostol will be obtained locally by each investigator as 200 μg tablets of commercially available misoprostol.

All study supplies will be kept in a locked, dry cabinet.

5.4 Labeling

A) Mifepristone — Mifepristone will have a label which will include product identification, expiration date, and drug dose. In addition the following will be printed on the labels: CAUTION: New drug. Limited by Federal Law to Investigational Use. All medication packets will be labelled with the protocol number.

B) Misoprostol — Misoprostol will be obtained locally by each investigator as 200 μg tablets of commercially available misoprostol and dispensed from the center pharmacy.

5.5 Concomitant Medications

No salicylates, indomethacin, or any other drug which inhibits prostaglandin synthesis should be taken. If necessary, analgesics belonging to other pharmacologic classes or spasmolytic drugs may be used. Drugs such as trifluoperazine and related phenothiazines (for treatment of nausea and vomiting) that could increase the risk of hypotension must be avoided as should oxytocin and any other prostaglandin preparation.

The use of concomitant medications during the course of this study will be recorded in the Case Report Form, and these data will be analyzed.

6. STUDY PROCEDURES

Each participating study center will record on a daily basis the number of subjects recruited in each of the three groups. All women approached to participate in the study will be recorded in the study data. Those who refuse to participate in the trial will have a special form completed for the database. These data will be communicated to the sponsor on a weekly basis. At each center, the number of subjects recruited into each of the groups will be equal to one-third the total assigned to the center if possible. When any of the groups has been filled, no further recruitment into that particular group will be conducted. Under no circumstances will any member of the study center staff suggest that a subject appearing at the center, with a duration of amenorrhea consistent with a completed group, be deferred in her request for pregnancy termination to allow for enrollment into an open group at a later time.

6.1 VISIT 1 (Admission, Day 1 of Study)

At the time of the subjects enrollment (Day 1), all the following should be done:

- Counseling.
- Medical, obstetrical and gynecological history.
- Medical examination, including: height, weight, blood pressure, and pulse.
- Bimanual pelvic examination.
- Urine pregnancy test.
- Quantitative Serum ßhCG.
- Vaginal ultrasound.
- Determination of Rh status and where routinely collected, the blood group.
- Hemoglobin or hematocrit determination.

Blood samples will also be collected prior to the administration of mifepristone for the following:

Chemistry Panel (4mL)
Which includes:

Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Total Bilirubin, Blood urea nitrogen, Phosphate, Creatinine, 24 hour fasting Glucose, Albumin, Lactate dehydrogenase, Potassium, Sodium, Chloride, Bicarbonate, Uric Acid, Calcium, as well as Cholesterol, Triglycerides, and Total Protein

Hematology Panel (3mL)
Which includes:

Hemoglobin, Hematocrit, RBC, WBC with differential, Platelet count*

Food should be withheld for one hour prior to and one hour post administration of the study drug. At admission to the study, the three tablets of mifepristone (600 mg total) will be swallowed by the subject with no more than 240 mL of water in the presence of a member of the center's study staff who will record the date and time of the administration.

Subjects who smoke will be instructed to refrain from smoking until after the administration of misoprostol at Visit 2, and an appointment will be made for Visit 2.

Subjects will be given a copy of the informed consent and patient diary card describing symptoms which require emergency treatment. These include: heavy bleeding, fever, and severe abdominal pain. The subjects will be given the address and 24 hour telephone number of a medical center (including the name of physicians) which cares for patients on a 24 hour a day basis.

A diary will be provided to each of the subjects for recording medications and symptoms, such as pain, nausea, vomiting and diarrhea. The diary will also be used to record the occurrence of vaginal bleeding on each day. The subject will be instructed to record the bleeding relative to their normal menstrual flow (e.g., lighter, the same as or heavier than normal). If the expulsion takes place before Visit 2, the date and time should be recorded on the subjects diary.

* Amendment 2 dated April 27, 1995.

6.2 VISIT 2 (Prostaglandin Administration, Day 3 of Study)

Visit 2 will be conducted on Day three (3) of the study. The following will be performed:

- Clinical examination.

- If the patient believes that expulsion occurred prior to Visit 2, the date and time will be recorded on the case report form as they were noted in the subjects diary. Since it is difficult to confirm that an abortion at this time is complete, nearly all subjects will require misoprostol. If however, the physician can verify unequivocally that complete abortion has occurred, the misoprostol will not be administered. If the abortion is incomplete or if there is any uncertainty about the completeness of the abortion, the misoprostol will be administered.

- Brief interview and review of the diary.

- Any adverse events which occurred since Visit 1 will be recorded on the case report form.

- Subject will receive an injection of anti-D globulin if the subject is Rh negative, if indicated.

- Food should be withheld for one hour prior to and one hour post the administration of misoprostol. The two tablets of misoprostol (400 μg total) will be swallowed by the subject with no more than 240 mL of water in the presence of a member of the center's study staff who will record the date and time of the administration.
- The subject will be observed at the study center for the four hour period post the administration of misoprostol at a minimum. The facility should be capable of surgical termination of pregnancy (by vacuum aspiration or dilation and curettage) and have access to blood transfusion and emergency resuscitation.

- During the observation period, the following should be recorded at least hourly:

- Occurrence of nausea, vomiting, or diarrhea. Intensity should be recorded as:

0: none
1: mild
2: moderate
3: severe

Any treatment for these will be recorded as concomitant medications.

- At the onset of any abdominal pain, the following will be recorded:

Intensity, recorded as: none, mild, moderate, or severe.

Duration, documenting any treatment as a concomitant medication.

- Blood pressure and heart rate at hourly intervals unless more frequent readings are indicated.

- Time of expulsion, if occurring during the observation period.

- Any unexpected symptom or clinical finding.

The use of intramuscular sulprostone in combination with mifepristone in previous studies has occasionally precipitated an episode of hypotension usually associated with bradycardia. In extremely rare circumstances this previously utilized treatment regimen has been associated with myocardial infarction and ventricular tachycardia. These complications are very unlikely with the combination of misoprostol and mifepristone. However, any significant fall in blood pressure or significant change in heart rate, however transient, following the administration of misoprostol will be recorded and the subject observed for at least three hours after their blood pressure and heart rate have returned to baseline. In case of chest pain, hypotension or cardiac arrhythmia, an ECG should be performed immediately and if required adequate resuscitation should be undertaken.

The cycle immediately following the administration of mifepristone is ovulatory. Therefore, subjects will be counseled to initiate contraception. Barrier contraception may be initiated within three days of misoprostol administration.

- A gynecological examination will be performed to determine if products of conception remain in the vagina or cervix.

- A very active attempt should be made to contact any subject who fails to appear for the Visit 2 appointment. The administration of misoprostol after Day 3 is strongly discouraged. Misoprostol may be administered between 36 and 60 hours after mifepristone administration.

- If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.

6.3 VISIT 3 (Exit Interview, Day 15 of Study)

Visit 3 will be conducted on Day fifteen (15) of the study. At Visit 3 the following will be performed:

- Clinical and gynecological examination.

- Assessment of severity and duration of uterine bleeding. Subjects who experience bleeding post Day 15 should be followed-up via telephone until the bleeding has stopped or intervention is clinically indicated.

- Assessment of hemoglobin or hematocrit if indicated.

- Blood samples will be collected for:

Chemistry Panel (4mL)
Which includes:

Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Total Bilirubin, Blood urea nitrogen, Phosphate, Creatinine, 24 hour fasting Glucose, Albumin, Lactate dehydrogenase, Potassium, Sodium, Chloride, Bicarbonate, Uric Acid, Calcium, as well as Cholesterol, Triglycerides, and Total Protein

Hematology Panel (3mL)
Which includes:

Hemoglobin, Hematocrit, RBC, WBC with differential, Platelet count

A total of twelve (12) subjects per each group of amenorrhea duration, for a total of thirty-six (36) per center will be involved in these assessments at six (6) selected centers. Thus, a total of 216 subjects from the entire study population will participate.*

- Verification of any concomitant medications or other therapeutic measures since Visit 2.

*Amendment 2 dated April 27, 1995

- Assessment of expulsion (history, pelvic examination), as well as date and time of occurrence if appropriate.

- Final evaluation of the treatment outcome through the clinical and gynecological examination. If necessary, perform ultrasonography and/or urine pregnancy test.

- In instances where the medical abortion method has failed, either completely or partially, perform the necessary additional surgical procedure. In the subjects for whom a surgical procedure is required, schedule a follow-up visit as per Section 6.6 below.

- Examine the subject's view of her abortion experience including her view of the experience relative to expectations; assessment of discomforts and side effects; timing and place of abortion; satisfaction with the experience; comparison to any previous abortion experience; best and worst features of the method being assessed in the trial; attitude toward self-administration of prostaglandin at home and preference for home or clinic treatment. All responses will be recorded in the case report forms.

- Assure that the subject's case record forms have been completely, accurately and properly filled in.

- A very active attempt should be made to contact any subject who fails to appear for the Visit 3 appointment.

- If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.

6.4 UNSCHEDULED VISITS

At Visits 1 and 2, subjects will be advised that they may return to the study center at any time if they experience medical problems associated with the medical abortion or for any other medical problem. At any unscheduled visits the following will be recorded:

- Reason for the visit.

- Use of any concomitant medications since the last visit.

- Information regarding utilization of any other medical resources.

- Pregnancy status at onset of visit.

- Temperature, blood pressure, heart rate, and hemoglobin.

- Any medication administered during visit as well as any medications prescribed.

- Any procedures conducted during the visit.

- Results of any pathology testing.

Subjects who have a surgical abortion at any unscheduled visit will have the exit interview (As defined in Section 6.3 above) prior to departure from the study center on the day of the surgical abortion, and will not return for the scheduled Visit 3. However, subjects undergoing surgical abortion will be scheduled for a follow-up visit as outlined in Section 6.6 below.

6.5 MEDICAL ADVISORY COMMITTEE

If serious adverse events occur beyond expectation, the decision of whether or not the study should be discontinued or modified will be taken by the Sponsor in consultation with the Medical Advisory Committee.

6.6 FOLLOW-UP

Subjects who are enrolled and receive either or both drugs in the study and undergo surgical abortion at any time during their enrollment will be scheduled for a follow-up visit. This follow-up visit will be scheduled for two weeks post the date of the surgical abortion. At this visit the following will be recorded:

- Brief medical history and clinical examination.

6.7 EARLY WITHDRAWAL FROM THE TRIAL

Subjects may withdraw from the study at any time at their own request. In all cases, the reasons for the subjects withdrawal must be recorded in detail in the case report forms and in the patients medical records. In all cases of withdrawal the subjects must be encouraged to have surgical abortions. If any subject refuses surgical abortion, the investigator must record that the subject understands the

risks involved in allowing the pregnancy to continue once drug treatment has begun. **A center must retain its records with respect to a subject who withdraws from the study after ingesting mifepristone and for whom a complete abortion has not been confirmed for a period of at least 30 years following the subject's last visit to the center.**

All efforts will be made to contact subjects who fail to return for the necessary visits (telephone, registered mail). The subject will not be given misoprostol if contacted after 60 hours of the study. A subject may not complete the treatment regimen if severe side effects or symptoms develop after mifepristone administration that, in the opinion of the principal investigator, constitute a threat to the woman's health. Any subjects who do not complete the treatment regimen for any reason will be assessed for the completeness of the abortion, if possible. Any subject who has received mifepristone and has at the time of early termination had an incomplete abortion, as described above, will undergo surgical abortion as described in Section 6.3 above, and will be considered a failure.

7. ADVERSE EXPERIENCES

7.1 General Aspects

Adverse Reactions

Subjects will be notified of possible adverse reactions; they will be instructed to immediately report all adverse reactions to the investigator.

Any adverse reaction, noticed by the investigator or reported by the subject, including clinically significant lab abnormalities, will be recorded in the appropriate section of the case report form, regardless of its severity and relationship to study drug.

Serious or unexpected adverse events will be immediately reported by the investigator by telephone to:

Dr. Irving Spitz
Dr. C. Wayne Bardin
The Population Council, Inc.
(800) 327-8730
24 hour answering service outside normal business hours

—— will notify the sponsor, and ensure FDA notification. All serious ("any experience that is fatal or life-threatening, is permanently disabling, incapacitating, requires inpatient hospitalization, or causes a congenital anomaly, cancer or is due to overdose") and/or unexpected ("any adverse experience that is not identified in nature, severity or frequency in the current investigator's brochure for the study") adverse

reactions must be immediately (within 24 hours) reported by telephone to the Sponsor and a written report must be submitted to the medical monitor within 24 hours.

The initial telephone contact will be followed within 3 days by a detailed report of the event which will include copies of hospital case reports, autopsy reports and other documents, when applicable. The adverse event must be followed through resolution.

The same applies to all subjects who died during the course of the study or within 30 days of completion of treatment irrespective of whether the adverse reaction was judged as related to treatment. In case of a death, copy of the autopsy report should be sent to the sponsor, if performed.

For each adverse reaction, the following information will be entered in the case report form: description of event, onset date, resolution date, severity (1=mild, awareness of sign or symptom, but easily tolerated; 2=moderate, discomfort enough to cause interference with usual activity; 3=severe, incapacitating with inability to do usual activity), drug cause-effect relationship and the outcome of the event. The investigator will also note if any action was taken regarding the test drug (temporarily or permanently discontinued) and if therapy or hospitalization was required.

ETHICAL ASPECTS

A. Informed Consent Form

The purpose of the study, those adverse reactions that are known to occur with the study drugs and the subject's right to withdraw from the study at any time without prejudice, must be explained to each subject in a language she understands. The subject is then required to sign in the presence of a witness an approved informed consent form in a language she understands containing all the above-mentioned information and a statement that the subject will permit examination of his/her study case report forms by a third party. Willing subjects may be interviewed by a representative of the sponsor about her understanding of the risks, benefits, procedures, and the experimental nature of the study.

B. Institutional Review Board

This study will not be initiated until the protocol and informed consent form have been reviewed and approved by a duly constituted Institutional Review Board (IRB) as required by U.S. FDA regulations. It is the responsibility of the investigator to submit the study protocol with its attachments to the IRB for review and approval.

The names and professional affiliations of all the members of the board or the IRB general assurance number must be given to the Sponsor of the study prior to study initiation, along with a signed and dated statement that the protocol and informed consent form have been reviewed and approved by the IRB.

The investigator is committed, in compliance with FDA regulations, to inform the IRB of any emergent problems, serious adverse reactions or protocol amendments.

C. Protocol Amendments

Any amendment to the protocol will be with mutual agreement between the investigator and the Sponsor. All amendments to the protoeol will be submitted to the FDA and to the Institutional Review Board (IRB) concerned for review and, if necessary, approval prior to implementation of the changes.

D. Study Monitoring

A pre-study visit will be made by the monitor to the investigative site in order to review the protocol and to ascertain that the facility is adequate for satisfactory conduct of the study, as well as to discuss the obligations of both the sponsor and the investigator.

The investigator will permit a representative of the sponsor or his designate and the FDA, if requested, to inspect all case report forms and corresponding portion of the study subjects original office and/or hospital medical records, at regular intervals throughout the study. These inspections are for the purpose of assessing the progress of the study, verifying adherence to the protocol, determining the completeness and exactness of the data being entered on the case report forms and assessing the status of study drug storage and accountability. During site visits, case report forms will be examined by the study monitor(s) and verified by comparison with corresponding source data (such as hospital and/or office records).

ADMINISTRATIVE ASPECTS

A. Curricula Vitae

The investigator will provide the Sponsor with copies of the curricula vitae of himself/herself and the co-investigators listed on the FDA Form 1572.

B. Data Collection in the Case Report Form

A Case Report Form in triplicate will be provided by the sponsor for each subject to be filled in at each visit. Additional forms will be used for screening of the subjects prior to enrollment. In the event of additional visits, extra case report forms for the unscheduled visits will be filled out. At the visits on Days 1 and 15, acceptability questions will be asked, and the data recorded.

Acceptability questions will be asked on the day of surgical abortion for those having a surgical abortion.

One copy of the forms will be retained by the clinical study site, the other copies will be retrieved by the study monitor at the monitoring visits. All forms will be filled in legibly in black ball point pen. All entries, corrections and alterations are to be initialed and dated by the investigator, co-investigator, or study coordinator making the correction. Corrections will be made by crossing through the incorrect data with a single line so that the incorrect information remains visible, and putting the correct information next to the incorrect data. A reasonable explanation must be given by the investigator for all missing data.

C. Data Retrieval

At intervals during the study and at the conclusion of the study, the study monitor will retrieve signed and dated case report forms from the study site for data entry and analysis. The original and one copy of each page will be retrieved by the monitor. The investigator will keep a copy of all original case report forms and source documents.

D. Records Retention

Except as otherwise explicitly set forth herein, pursuant to applicable federal regulations, the investigator must retain copies of all study records for a period of two (2) years following the date a marketing application is approved for the indication for which the drug is being investigated. If no application is filed or if the application is not approved, the study records must be retained until 2 years after the investigation is discontinued and FDA is notified.

E. Study Termination

Either the investigator or the sponsor may terminate the study at any time for well documented reasons, provided a written notice is submitted at a reasonable time in advance of intended termination.

8. STATISTICAL ANALYSIS

8.1 Population Analyzed

All subjects to whom mifepristone has been administered will be included in the analyses.

A) Efficacy

Efficacy will be determined by each subject's abortion status and history at Visit 3 (Day 15), two weeks post the administration of mifepristone. The pregnancy/abortion status requires a clinical evaluation, including where necessary ultrasonographic and/or urine pregnancy results.

One measure of success will be defined as a pregnancy termination by Visit 3 (Day 15) without the need for surgical or instrumentation procedures except for forceps extraction of ovular tissue fragments extending through the external cervical os. If pregnancy has not been terminated by Visit 3 (Day 15), this will be considered a failure.

FAILURES

Two categories of failures will be recognized. These will be called medical failures and acceptability failures.

Medical failures are of two types:

i) persisting pregnancy at Visit 3 (Day 15).
ii) medically indicated surgical intervention because of:
    a) incomplete expulsion at Visit 3 (Day 15).
    b) serious adverse advents that warrant early surgical interruption of pregnancy.

Acceptability failures are deemed to have occurred when subjects request surgical interruption of a persisting pregnancy before Visit 3 (Day 15) without medical necessity.

In consequences of this distinction between types of failure, there will be two evaluations of success and failure rates.

The *medical failure rate* (MFR) will be determined by life table analysis on a day to day basis from Visit 1 (Day 1) through Visit 3 (Day 15). Women who request surgical abortions before Visit 3 (acceptability failures) will be considered as censored as of mid-day on the day of the surgical abortion. Persisting pregnancies as of Visit 3 are considered failures. The method success rate is 1-MFR for any day or cumulative analysis. Women with persisting pregnancies of less than two weeks post the administration of mifepristone when last observed (e.g., lost to follow-up) will be treated as censored in mid-day of the last observation in the calculation of gross rates.

The *total failure rate* (TFR) will also be determined by life table techniques using the assumption that some of the subjects with persisting pregnancies are last observed before two weeks post the administration of mifepristone. Daily total failure rates are computed under the assumption that subjects with continuing pregnancies last observed before Visit 3 were last observed in the middle of the day of last observation.

Data will be recorded in the case report forms to allow for the distinction between medical and acceptability failures.

All failures will undergo vacuum aspiration or dilation and curettage. Material will be submitted for pathological examination.

B) Safety

Safety will be assessed utilizing the following parameters:

- Duration and severity of uterine bleeding; data obtained from subject diary, determination of hemoglobin, by treatment (e.g., transfusion, surgical procedure) necessary secondary to heavy and prolonged uterine bleeding.

- Occurrence of any adverse event or abnormal clinical finding (e.g., signs of pelvic infection).

- Adverse events linked to drug administration and abortion (e.g., nausea, vomiting, diarrhea, painful uterine contractions).

- Assessment of heart rate and blood pressure during the observation period following the administration of misoprostol.

Safety data will include all safety parameters at all visits both scheduled and unscheduled, as well as data collected in the subject's diary, of all subjects to whom mifepristone has been administered.

C) Acceptability

Acceptability will be measured by patient interviews at the final discharge visit. The assessments will be made on the basis of answers to questions concerning:

- satisfaction with the information and counseling,
- satisfaction with the procedure,
- comparison to previous abortion experience, where applicable,
- willingness to choose the method again, and,
- willingness to recommend the method to others.

All these variables will be assessed in light of the level of complications, discomforts, and side effects recorded for each patient on both the questionnaire and symptomatology diary.

Acceptability of the regimen will also be determined through a questionnaire for providers.

D) Feasibility of Use in the U.S. Health Care System

Variability is built into the study with regard to: Type of abortion site (hospital clinic, Planned Parenthood clinic, feminist health clinic, private practice, free-standing abortion clinic), ethnicity of patient, socioeconomic status (Medicare, self-pay, insurance, help fund, etc.), and location in inner city, small city, suburb, or rural area. The association of these factors with:

- adherence to the protocol
- complications and side effects
- failure (and type of failure)
- patient satisfaction with medical abortion
- provider comfort with medical abortion

will be analyzed.

8.2 ANALYTIC METHODS

8.2.0. A detailed plan, outlining in advance the statistical evaluation of each baseline, safety and efficacy variable, will be submitted to file prior to statistical examination of the data. Essential features of this plan, as presently anticipated, are described below.

8.2.1. Descriptive Statistics: Characteristics of subjects measured at admission through the administration of mifepristone will be summarized. All variables pertaining to safety, efficacy and acceptability will be summarized.

8.2.2. Lifetable Analysis of Efficacy: Single and multiple decrement failure rates for each type of failure and for the total failure rate will be analyzed for each amenorrhea duration, and all durations. Failure rates, by duration of amenorrhea, for age, ethnic group, payment status, and service delivery groups will be determined.

8.2.3. Efficacy Analysis: Multinomial logistic models will be employed to evaluate efficacy. Successful abortion, incomplete expulsion, early surgical interruption due to medical necessity and early surgical interruption at the patient's request (no medical necessity) will serve as the outcome categories used to form response vectors for the models. In one model, the response vector will be comprised of the cumulative log odds over the three types of failure (i.e., incomplete expulsion, medical interruption and requested interruption). In another model, the response vector will be the log odds of these individual types of failure *per se*. In all models, the independent vector will be amenorrhea duration ($\leq$ 49 days, 50-56 days and 57-63 days).

The models will be used to test the overall (omnibus) effect of amenorrhea status. Additionally, pairwise contrasts among the amenorrhea groups will be evaluated. Both the overall effect and pairwise effects will be examined using traditional hypothesis tests to assess the *complete response vector* (i.e. all failure categories considered simultaneously). However, *individual response categories* will be examined in two ways. First, a traditional hypothesis test will be used to conduct a test of the overall affect of amenorrhea. Second, the examination of pairwise amenorrhea group contrasts will take the form of an equivalency test.

All traditional tests will be evaluated using a type I error rate of 0.05. Equivalence tests will be performed using 90% confidence intervals (which mathematically correspond to a type I error rate of 0.05) and an equivalence interval of $\pm$ 5 percentage points.

Single and or multiple decrement life table techniques, as appropriate, will be used to display failure rate probabilities by time, for individual amenorrhea group and all groups combined.The various effects examined using the multinomial logistic models will also be exhibited in tables and/or figures.

8.2.4. Analysis of factors associated with early abortion (Days 1-3) or late abortion (Days 4-15) or Failure will be undertaken by a variety of multivariate techniques. This analysis pertains to aspects of efficacy, safety and acceptability.

8.2.5. Baseline/Safety Analysis. Qualitative baseline and safety variables will be systematically summarized in appropriate patient groupings for examination by the medical reviewer. Descriptive statistics for baseline and safety variables that are suitable for quantitative analysis will be displayed in tables and figures. Furthermore, these variable will be evaluated across amenorrhea groups using linear models, applied to continuous or categorical variables. Continuous variables expected to markedly deviate from normality will be rank transformed to obtain nonparametric tests of significance. Any baseline variable found to exhibit a meaningful difference across amenorrhea groups, will be considered for use as covariate or blocking factor in the efficacy analysis. As a conservative measure to increase statistical power, variables exhibiting p-values of 0.20 or less will be singled out to assess their potential relevance to the safety and efficacy of the study drug.

Analysis of variables associated with need for transfusion and with severe cardiovascular adverse events will be undertaken.

8.2.6. Acceptability Analysis: Analysis of variables associated with acceptability within each duration of amenorrhea and overall shall be undertaken using both univariate and multivariate techniques.

9. RISK-BENEFIT ASSESSMENT

Experience gained to date with the use of mifepristone and prostaglandin for the termination of early pregnancy indicates that this has few side effects and a frequency of short-term complications that is comparable to that observed after vacuum aspiration. The most common complaints during treatment, particularly following administration of the prostaglandin, are lower-abdominal pain, nausea, vomiting and diarrhea. In addition, bleeding for several days is common. For these complaints, appropriate medication can be prescribed when required. Occasionally, heavy uterine bleeding may necessitate emergency curettage and, very rarely, blood transfusion.

The approximate failure rate, according to the experience gained from women who have had this treatment in Europe, up to 49 days is 5%. Therefore approximately 5% of the subjects in this trial treated up to 49 days of amenorrhea will be expected to undergo surgical termination of pregnancy. It is possible the failure rate will be higher in the older pregnancies. **Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women with amenorrhea of no more than 49 days before administration of mifepristone.**

[ ]

There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. This excess bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea.**

Following a treatment regimen involving the intramuscular injection of the prostaglandin analog sulprostone, in a very low percentage of cases (one in 20,000), serious cardiovascular complications have been observed, including one case of fatal myocardial infarction. These complications have been most often associated with subjects who were heavy smokers, and still these complications are extremely rare. There is no evidence that misoprostol, a different class of prostaglandin, which is widely prescribed for longterm use in the prevention and treatment of peptic ulcer disease, is associated with any such cardiovascular side effects.

All subjects will be informed as to the potential complications. Centers participating in the trial will ensure that qualified personnel and necessary equipment and supplies are available at all time to deal with any complications.

Studies conducted in mice and rats have shown that mifepristone does not have any teratogenic effects. There are insufficient data to evaluate the effects of mifepristone on the human fetus. In one subject in France who took mifepristone and failed to abort, pregnancy was terminated at 18 weeks because of fetal abnormalities. The precise relationship to mifepristone could not be established[6]. Thus, in the event of a continuing pregnancy, surgical abortion should be performed. Misoprostol has been reported to be teratogenic and is reported to be associated with malformations of the scalp, cranium and other abnormalities[7].

The benefits of this form of medical termination of pregnancy are that most women participating in the study can be expected to have a complete abortion and will not be exposed to the risks associated with surgical abortion, particularly the risks of physical trauma (e.g., cervical laceration, uterine perforation, etc). Nor does medical abortion carry any anesthetic-related risk.

No financial renumeration will be offered to potential study participants.

**Amendment 3 dated May 2, 1995

10. SIGNATURES

I have read the forgoing protocol and agree to conduct the study as outlined.

_____	____/____/____
Signature of Investigator	M D Y
_____	____/____/____
Signature of Sponsor	M D Y

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Table 1

	Visit 1	Visit 2	Visit 3
Counseling	X		
Medical, OB-GYN History	X		
Medical Examination	X	X	X
Pelvic Examination	X	X	X
Urine Pregnancy Test	X		X*
Quant. Serum ßhCG	X		X*
Vaginal Ultrasound	X	X*	X*
Blood Typing including Rh	X		
Hemoglobin or Hematocrit Determination	X		X*
Administration of Mifepristone	X		
Administration of anti-D globulin		X*	
Administration of Misoprostol		X	
Interview and Review of Diary		X	X

* - To be conducted if indicated

References

1. Spitz, I.M. and Bardin, C.W., "RU 486-A modulator of progestin and glucocorticoid action," *N Engl J Med*, pp. 404-12, 1993.

2. Ulmann, A., Silvestre, L., Chemma, L., Rezvani, Y., Renault, M., Aguillaume, C.J., and Baulieu, E.E., "Medical termination of early pregnancy with mifepristone (RU 486) followed by a prostaglandin analogue," *Acta Obstet Gynecol Scand*, vol. 71, pp. 278-83, 1992.

3. Klitsch, M., "Antiprogestin and the abortion controversy. A progress report.," *Fam. Plan. Perspectives*, vol. 23, pp. 275-81, 1991.

4. Peyron R., Aubeny, E., Targosz, V., Silvestre, L., Renault, M., Elkik, F., Leclerc, P., Ulmann, A., and Baulieu, E.E., "Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol," *New Engl. J. Med.*, vol. 328, pp. 1509-1513, 1993.

5. Thong, K.J. and Baird, D.T., "Induction of abortion with mifepristone and misoprostol in early pregnancy,:" *Br. J. Obstet. Gynaecol.*, vol. 99, pp. 1004-7, 1992.

6. Pons, J.C., Imbert, M.C., Elefant, E., Roux, C., Herschkorn, P., and Papiernik, E., "Development after exposure to mifepristone in early pregnancy," *Lancet*, vol. 338, p. 763, 1991.

7. Fonesca, W., Alencar, A.J.C., Mota, F.S.B., and Coelho, H.L.L., "Misoprostol and congenital malformations," *Lancet*, vol. 338, p. 56, 1991.

APPENDIX 1

PROTOTYPE INFORMED CONSENT

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 B

1. Purpose and aims of the study

It is possible to induce abortion in women with unwanted pregnancies by taking mifepristone in combination with a prostaglandin (misoprostol). Mifepristone is a drug which blocks the action of progesterone, a hormone needed to maintain pregnancy. One of mifepristone's actions is to interrupt pregnancy in its early stages. Prostaglandins are natural substances made by the lining of the womb during menstruation and cause contraction of the womb. **Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women whose first day of their last menstrual period occurred no more than 49 days before administration of mifepristone.**

[ ]

There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea**

Major advantages of this method of pregnancy termination are that no surgical instruments are pushed into the womb. Over 150,000 women in 20 countries have used mifepristone and a prostaglandin as a medical method of pregnancy interruption. Mifepristone and misoprostol have been used by over 50,000 women at the dose to be used in this study. The dosage to be studied has been approved for routine use in France for women who have been pregnant for seven weeks or less. Mifepristone in combination with a prostaglandin has also been approved for use in China, Britain and Sweden. In the latter two countries, it is used in women who are pregnant for nine weeks or less.

**Amendment 3 dated May 2, 1995

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS*

PROTOCOL NUMBER: 166 B

The aims of the present study are to determine the safety, efficacy and acceptability of mifepristone plus misoprostol for pregnancy termination in women who are 63 days or less from the first day of the last menstrual period. Three groups of women who are less than 50 days; 50 through 56 days and 57 through 63 days from the first day of the last menstrual period will be included in the study. This study is being performed as a requirement for registration of mifepristone plus misoprostol with the U.S. Food and Drug Administration (FDA) so that these products can be used for pregnancy termination in the U.S.

2. Clinic visits

I understand that at my initial visit (visit 1) I will receive counseling about the method, and a urine and blood sample will be collected to make sure I am pregnant. I will be given a physical, and a pelvic exam and my medical history will be taken. Using a vaginal ultrasound, which is a small probe that is placed in the vagina, the duration of my pregnancy will be determined. Also I will be given a blood test for the Rh factor in my blood. If I have an Rh negative blood type, I will be given an injection at the second visit to prevent the development of antibodies that could endanger any future pregnancy. **I understand that I may be asked for additional blood samples (about 2 teaspoons) to be collected to measure the levels of different substances normally in my blood, as well as determine the normal characteristics of my blood. If I decide not to have additional blood samples taken, I may still continue to participate in the study* .** In order to terminate my pregnancy, I will take three tablets of mifepristone (first medication) orally in the presence of study personnel. Two days later, I will return to the clinic (visit 2) even if I believe I have aborted and will take two misoprostol tablets (second medication) by mouth if I have not aborted. If I take the second medication, the duration of my stay at the clinic at the second visit will be approximately four hours, during which time I will be closely monitored by the study team. During this time, there is an 60-80% chance that abortion will occur. If I come to the clinic in a car, I will be sure to arrange for someone else to drive me home from this visit, and understand that I will not drive myself home.

* Amendment 2 dated April 27, 1995

dment 3
5, 1995

*EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND * MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS*

PROTOCOL NUMBER: 166 B

I understand that if the abortion does not occur at the clinic, it is likely to occur at home and I may continue to have uterine bleeding for several days. **I understand that the amount of bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The risk of heavy bleeding increases after 49 days since the first day of my last menstrual period**** . I should use sanitary napkins until the uterine bleeding or spotting ends and not use tampons. As with surgical abortion, I cannot resume douching until the bleeding stops (about 10-12 days). I should not resume sexual intercourse for eight to ten days after taking the prostaglandin, by which time most abortions would have been completed.

I understand that I may see the product of conception on my sanitary napkin or in the toilet. This may happen at the clinic, at home or work. Through the seventh week after conception, this product is called an embryo; it is smaller than a quarter and is usually embedded in a blood clot. Even if I see the products of conception, I will not be able to tell whether the method has been effective as part of the placenta may still remain in the uterus. This is why it is important to return to the clinic for a follow-up, visit 3, so that the clinic staff can determine if the abortion is complete.

A further appointment will be made for me to return to the clinic two weeks after taking the first tablet (visit 3), to ensure that the treatment has been effective. **I understand that I may again be asked for additional blood samples (about 2 teaspoons) to be collected to measure the levels of different substances normally in my blood, and to determine the characteristics of my blood. If I decide not to have additional blood samples taken, I may still continue to participate in the study.*** If the treatment has not been effective, then a surgical procedure called vacuum aspiration or dilatation and curettage will be carried out at that time to complete the abortion. This is the same

** Amendment 3 dated May 2, 1995

* Amendment 2 dated April 27, 1995

surgical procedure that would have been used had I elected to undergo surgical abortion in the first instance. I will be sure to have arranged for someone else to drive me home from this visit, and understand that I will not drive myself home. If I notice a vaginal discharge with odor after treatment, this may indicate an infection. I will contact my physician for an appointment.

I understand that bleeding may continue beyond my third visit. If this occurs the clinic will contact me by telephone to determine if it has stopped or if I need additional treatment.

I understand that there are no indications at present that use of an antiprogestin to end a pregnancy has prevented or harmed a woman's ability to have a baby in the future. Women who have taken mifepristone have been able to conceive and subsequently bear a healthy child. Since it is possible to become pregnant again after the abortion, I will be asked to select and use a contraceptive method.

3. Benefits

I understand that an advantage of the mifepristone/misoprostol medical method for pregnancy termination is that it avoids a surgical procedure. There is no anesthesia-related risks or risk of uterine perforation or cervical canal injury which may rarely be observed after surgical termination of pregnancy. Another benefit is the satisfaction of participating in the study that will make mifepristone/misoprostol available to women in the U.S.

4. Risks and discomforts

I understand that drawing blood for the tests at the first **and third visits** may be associated with discomfort, bruising, and possibly infection at the site of withdrawal. I understand that experience gained so far with the combination of drugs and the termination of early pregnancy indicates that this therapy has few side effects. The frequency of short-term complications are comparable to that observed after surgical abortion performed by vacuum aspiration. The most common complaint during treatment (particularly following administration of the second medication) is lower abdominal pain or cramps which are similar to those associated with a very heavy menstrual period. I will receive appropriate medication for pain when required.

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS*

PROTOCOL NUMBER: 166 B

I understand that I should not take aspirin, Motrin®, ibuprofen (Advil®) or any other drug known to block the action of prostaglandins. However, I may take Tylenol® and I may receive stronger medications for pain from my doctor. I understand that cramps and abdominal pains are usual and an expected part of the abortive process. Nausea, vomiting, and diarrhea have been observed following administration of the second medication. Therefore, at the second visit it is necessary to remain at the clinic under appropriate medical supervision for approximately four hours before returning home. **I understand that uterine bleeding, similar to that which occurs during a spontaneous miscarriage (i.e. more than a** heavy menstrual period) and lasting at least one week, may be expected. **The risk of heavy bleeding increases after 49 days since the first day of my last menstrual period**** In rare instances very heavy uterine bleeding may occur requiring surgical abortion and/or blood transfusion.

I understand that it is not advisable to allow a pregnancy to continue after taking mifepristone and/or misoprostol, since the full effects of mifepristone on the fetus are not known and misoprostol administration in early pregnancy has been associated with abnormal development of the fetus. I understand that based on prior studies and recently obtained information, abortion after mifepristone/misoprostol is successful in termination of pregnancy in approximately 95% of treated women whose first day of their last menstrual period occurred no more than 49 days before administration of mifepristone.

[ ]

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EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

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When abortion is incomplete, vacuum aspiration or dilatation and curettage are recommended to terminate bleeding and prevent anemia. *When abortion does not occur, surgical termination of pregnancy is recommended because of the possible risk to the fetus. I have previously agreed to this procedure.*

There have been no serious heart conditions in the 52,000 women using the combination of drugs in the study for pregnancy termination. However, serious cardiovascular complications, including one fatal heart attack occurred during medical abortion using a different drug combination. These heart conditions have occurred usually in women who are heavy smokers or have increased blood fats, diabetes, high blood pressure, or family history of heart disease. This risk also increased in women who are over 35 years of age. These complications have been seen only following an injected prostaglandin and are rare (one in 20,000 cases). To date there is no evidence that the oral prostaglandin (misoprostol) that I will be taking in this study and which has been used widely for prolonged periods of time in the prevention of stomach ulcers, is associated with such cardiovascular side effects.

5. Alternative Statement

I know that my pregnancy could be terminated by a surgically performed abortion procedure (dilatation and curettage or vacuum aspiration). The possible advantages and disadvantages of a surgical rather than a medical termination have been explained to me. The advantages of surgical termination of pregnancy is that this is a one day procedure. The risks associated with surgical abortion are minimal. These include the risk of an anesthetic procedure. In the U.S., less than 1% of patients who undergo a surgical abortion experience a major complication associated with the procedure such as a serious pelvic infection, cervical tear, bleeding requiring a blood transfusion or unintended major surgery (for a uterine perforation).

6. Physical Injury Statement

If I require medical treatment as a result of physical injury arising from my participation in this study, immediate, essential, short-term medical care and treatment as determined by the doctors in this study will be made available without charge to me. There will be no monetary compensation for any other care, but medical consultation and appropriate referral services are available. Further information on the availability of medical care and treatment for any physical injury resulting from my participation in this study may be obtained from the Investigator, Dr. _____ (telephone:_____).

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

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7. Whom to Call in an Emergency

I understand that if severe uterine bleeding, or abdominal pain, or any other medical emergency arises in association with this method, I will report immediately to (institute, address, telephone no.) In addition, I will contact Dr. _____

(telephone:_____). If he or she cannot be reached in a medical emergency related to the study, I may contact Dr. _____ (telephone:_____).

8. Offer to Answer Questions and Freedom to Withdraw from the Study

I have been told that I may withdraw from the study at any time without jeopardy to my present or future medical care from the hospital or clinic. If I withdraw I will be offered a surgical abortion. I have been told to contact Dr. _____(telephone:_____ or Dr. _____ (telephone:_____ if I have any questions about the research. These physicians may appoint their associates to answer my questions.

I also understand that the Principal Investigator may require me to withdraw from the study, if in his/her medical judgement it is in the best interest of my health or if it becomes impossible for me to follow the experimental procedure of this study.

I understand that, if my treatment under the study does not result in an abortion, and I refuse surgical abortion and continue with my pregnancy, I risk, and the infant may risk, complications, including fetal or infant malformation.

9. Confidentiality

I understand that information obtained in this study will be transmitted only in a form that cannot be identified with me, and that all records will be kept in a locked cabinet. I understand that the Population Council or their designated monitors, as well as the U.S. Food and Drug Administration may request access to my medical records.

I understand that I may be asked to be interviewed by a representative of the sponsor. The interview will be conducted in the language that I speak and will verify that I understand the risks, benefits, procedures, and the experimental nature of the study. If I do not agree to be interviewed, this will not affect my present or future medical care from the hospital or the clinic, or my participation in the study. I understand that I can change my mind at any time. All information will be kept confidential.

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EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 B

10. Subject's Statement

I, the undersigned, have had the risks and benefits of this study explained to me in a language that I understand. I agree to participate in this study as a volunteer subject.

_____ _____
Date Signature of Volunteer

11. Investigator's Statement

I, the undersigned, have explained to the volunteer in the language which she speaks the procedures to be followed in this study and the risks and benefits involved.

_____ _____
Date Signature of Investigator

_____ _____
Date Signature of Witness to the Above Signatures and Explanation

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AMENDMENT #1

Protocol:

Cover Sheet:	Change:	The Population Council to The Population Council, Inc.
	Change:	Written authorization from The Population Council, to written authorization **of** The Population Council
Table of Contents: 6.5:	Change:	~~_____~~ **to** MEDICAL ADVISORY COMMITTEE
P. 3: First paragraph:	The word either was added in reference to parenteral or vaginal prostaglandins in combination with mifepristone	
P. 3: Last paragraph:	Change:	heart condition **to** heart complications
P. 4: Third paragraph:	Change:	as <u>close</u> as possible to **as closely** as possible
P. 4: Last paragraph:	Add:	Subject shall visit the study center three times **unless state law requires an additional, initial informational visit with a mandatory waiting period before the process can begin.**
	Add:	At the initial visit (Day 1); **after any required statutory waiting period.**
P. 5: second paragraph:	Change:	institutional insurance **to** general liability insurance
P. 6:	Add: 4.1.3	**Residents of the United States**
P. 6:	Add: 4.2.9	**Resident of the United States**
P. 7: 4.3.2	delete	~~_____~~
P. 7: 4.3.5	Add:	**or hematocrit below 30%**
P. 7: 4.3.7	Delete	~~_____~~
	Add:	**Subjects with an IUD in place.**
P. 7: 4.3.15	Change to:	Women who cannot reach the source of emergency medical care that serves the abortion center within one (1) hour from (a) their home or place or work and (b) the abortion center.

P. 8: Section 5.2:		Clarification that 600 mg of mifepristone will be administered orally.	
P. 9: Section 5.3:	A)	Change to:	Mifepristone will be provided as 200 mg tablets of micronized mifepristone
	B)	Change to:	Misoprostol will be obtained locally be each investigator as 200 µg tablets of commercially available misoprostol.
P. 9: Section 5.4:	A)	Change to:	Mifepristone will have a label which will include product identification, expiration date, and drug dose. In addition the following will be printed on the labels: CAUTION: New drug. Limited by Federal Law to Investigational Use. All medication packets will be labelled with the protocol number.
	B)	Change to:	Misoprostol will be obtained locally by each investigator as 200 µg tablets of commercially available misoprostol and dispensed from the center pharmacy.
P. 9: Section 5.5 paragraph 1		Change: ——— to hypotension Change:	should be avoided to **must** be avoided
P. 10: Section 6.1:		Change:	Serum βhCG test to quantitative serum βhCG.
		Change:	Determination of blood group and Rh status to Determination of Ph status and where routinely collected, the blood group.
P. 10: Last paragraph:		Add:	**No more than** 240 ml.
P. 11: Second paragraph:		Change:	Subjects will be given written information **to** Subjects will be given a copy of the informed consent and patient diary card.
		Change:	.... which receives patients ..... **to which cares** for patients.
Section 6.2:		Add:	**If the patient believes that expulsion occurred prior to Visit 2, the date and time will be recorded on the case report form as they were noted in the subjects diary. Since it is difficult to confirm that an abortion at this time is complete, nearly all subjects will require misoprostol. If however, the physician can verify unequivocally**

			that complete abortion has occurred, the misoprostol will not be administered. If the abortion is incomplete or if there is any uncertainty about the completeness of the abortion, the misoprostol will be administered.
	Last paragraph:	Delete:	~~_____~~
		Add:	**, if indicated.**
P. 12:	First paragraph:	Add:	**No more than** 240 ml
	Second paragraph: Last sentence	Delete:	~~_____~~
P. 13:	Section 6.2: Second to Last paragraph	9/6/94 last paragraph Change to:	A very active attempt should be made to contact any subject who fails to appear for the Visit 2 appointment. The administration of misoprostol after Day 3 is strongly discouraged. Misoprostol may be administered between 36 and 60 hours after mifepristone administration.
P. 13:	Section 6.2:	Add:	**If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.**
P. 13:	Section 6.3:	Add:	**Subjects who experience bleeding post Day 15 should be followed-up via telephone until the bleeding has stopped or intervention is clinically indicated.**
P. 14:	after last paragraph:	Add:	**If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.**
P. 15:	Section 6.5:	Change Heading:	~~_____~~ Medical Advisory Committee.
		Change Body:	~~_____~~ Medical Advisory Committee

P. 16: Section 6.7: first paragraph	Add:	**A center must retain its records with respect to a subject who withdraws from the study after ingesting mifepristone and for whom a complete abortion has not been confirmed for a period of at least 30 years following the subject's last visit to the center.**
P. 16: Section 6.7: Second paragraph	Change:	——— 60 hours
P. 18: Section A:	Change:	study drug to study drugs.
P. 20: Section D:	Add:	**Except as otherwise explicitly set forth herein,**
P. 21: Seventh paragraph:	Change:	submitted for histological examination **to** submitted for pathological examination
P. 27:	Add:	**Hemoglobin or Hematocrit Determination, Quant. Serum βhCG**
	Change:	Administration of ——— **to** Administration of anti-D globulin

Informed Consent:

Section 1	Change:	——————— **to** over 150,000
Section 2 Clinic Visits: Second paragraph last sentence:	Change:	or third visit **to,** visit 3,
Section 2 Clinic Visits:	Add:	paragraph 4
		I understand that bleeding may continue beyond my third visit. If this occurs the clinic will contact me by telephone to determine if it has stopped or if I need additional treatment.

Section 8: After last paragraph

Add: **I understand that, if my treatment under the study does not result in an abortion, and I refuse surgical abortion and continue my pregnancy, I risk, and the infant may risk, complications including fetal or infant malformation.**

AMENDMENT #2

The protocol is being amended in order to determine if any changes occur in the blood chemistry or hematology parameters of subjects following the administration of mifepristone and/or misoprostol. Blood samples will be collected as outlined below.

The following additions to the protocol are indicated.

Blood samples will be collected prior to the administration of mifepristone at Visit 1 for the following: ***(page 10 of protocol)***

Chemistry Panel (4m*L*)
Which includes:

Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Total Bilirubin, Blood urea nitrogen, Phosphate, Creatinine, 24 hour fasting Glucose, Albumin, Lactate dehydrogenase, Potassium, Sodium, Chloride, Bicarbonate, Uric Acid, Calcium, as well as Cholesterol, Triglycerides, and Total Protein

Hematology Panel (3m*L*)
Which includes:

Hemoglobin, Hematocrit, RBC, WBC with differential, Platelet count

Blood samples will again be collected at Visit 3 (Day 15) for the ***same measurements listed (page 13 of protocol)*** above.

A total of twelve (12) subjects per ***each*** group ***of amenorrhea duration,*** for a total of thirty-six (36) per center will be involved in these assessments at six (6) selected centers. ***Thus,*** a total of 216 subjects from the entire study population will participate.

The notification process (contact and telephone number) Section 7.1 is modified to remove ~~telephone number~~ and

insert: **Dr. Irving Spitz or Dr. C. Wayne Bardin**
The Population Council, Inc.
(800) 327-8730

AMENDMENT #2 (INFORMED CONSENT)

The informed consent text was modified to reflect the additional blood collections for chemistry and hematology. ***(on pages 30, 31, 32)***.

Section 2 Clinic Visits

1st paragraph

..... could endanger any future pregnancy. *I understand that I may be asked for additional blood samples (about 2 teaspoons) to be collected to measure the levels of different substances normally in my blood as well as determine the normal characteristics of my blood. If I decide not to have additional blood samples taken, I may still continue to participate in the study.* In order to.....

3rd paragraph

..... treatment has been effective. *I understand that I may again be asked for additional blood samples (about 2 teaspoons) to be collected to measure the levels of different substances normally in my blood, and to determine the characteristics of my blood. If I decide not to have additional blood samples taken, I may still continue to participate in the study.* If the treatment.....

Section 4 Risks and Discomforts

1st paragraph, 1st sentence

..... for the tests at the first ***and third visits*** may be.....

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AMENDMENT #3

The protocol is being amended in order to reflect the recent data indicating an increased need for surgical procedures in Groups 2 and 3.

The additions to the protocol and informed consent are indicated.

Informed Consent

Page 25 **add:**

Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women with amenorrhea of no more than 49 days before administration of mifepristone. **There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. This excess bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea.**

Page 29 **delete:**

During the early stages of pregnancy, mifepristone plus misoprostol cause abortion in approximately 95 percent of women.

Page 29 **add:**

Recently obtained information supports the statement that mifepristone plus misoprostol cause abortion in approximately 95 percent of women whose first day of their last menstrual period occurred no more than 49 days before administration of mifepristone.

There are a number of reasons for such a surgical procedure including continued pregnancy, incomplete abortion, or excess bleeding. The possibility of experiencing excess bleeding increases with increasing duration of amenorrhea.

Page 31: Section 2

Add:

I understand that the amount of bleeding may be similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period). The risk of heavy bleeding increases after 49 days since the first day of my last menstrual period.

AMENDMENT #3 (con't)

Page 33: Section 4

Add:

I understand that uterine bleeding, similar to that which occurs during a spontaneous miscarriage (i.e. more than a heavy menstrual period) and lasting at least one week, may be expected. **The risk of heavy bleeding increases after 49 days since the first day of my last menstrual period.**

last paragraph

Add:

I understand that based on prior studies and recently obtained information, abortion after mifepristone/misoprostol is successful in termination of pregnancy in approximately 95% of treated women whose first day of their last menstrual period occurred no more than 49 days before administration of mifepristone.

[ ]

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THE POPULATION COUNCIL

Protocol 166A/B

CENTER NUMBER ____ ____

PATIENT NUMBER ____ ____ ____

PATIENT INITIALS ____ ____ ____

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ON ORIGINAL

CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____ DATE ____/____/____ M D Y

STUDY ENTRY CRITERIA

INCLUSION CRITERIA:

	(check one) No	Yes
1. Is the patient in good general health?	☐	☐
2. Is the patient 18 years of age or older?	☐	☐
3. Did the patient request a termination of pregnancy?	☐	☐
4. Does the patient agree to undergo surgical pregnancy termination in case of failure of the medical abortion method being evaluated?	☐	☐
5. Is the final estimate of duration of pregnancy based on 1) patient statement, 2) bimanual examination and 3) transvaginal ultrasound scan consistent with a time less than 64 days?	☐	☐
6. Does the patient have a positive urine pregnancy test?	☐	☐
7. Is the patient willing and able to participate in the study after its precise nature and duration have been explained?	☐	☐
8. Is the patient a resident of the United States?	☐	☐
9. Is the patient able and willing to sign an informed consent form? Date Signed: ____/____/____ M D Y	☐	☐

EXCLUSION CRITERIA:

	No	Yes
1. Does the patient have evidence of the presence of any disorder which respresents a contraindication to the use of mifepristone or misoprostol?	☐	☐
2. Does the patient have a history of severe liver, respiratory, or renal disease or repeated thromboembolism?	☐	☐
3. Does the patient have a history of cardiovascular disease?	☐	☐
4. Does the patient present with a blood pressure of >140 (systolic) or >90 (diastolic) or is the patient being treated for hypertension on a chronic basis?	☐	☐
5. Does the patient have a hemoglobin level below 10g/dL or hematocrit below 30% at the day 1 visit?	☐	☐
6. Does the patient use anticoagulants or have a known clotting defect?	☐	☐
7. Does the patient have an IUD in place?	☐	☐
8. Does the patient have insulin dependent diabetes mellitus?	☐	☐
9. Is the final estimate of duration of pregnancy based on 1) patient statement, 2) bimanual examination and 3) transvaginal ultrasound scan consistent with a time greater than 63 days?	☐	☐
10. Is the patient breast feeding?	☐	☐
11. Did the vaginal examination reveal adnexal masses or adnexal tenderness suggesting pelvic inflammatory disease?	☐	☐
12. Is there suspicion of ectopic pregnancy or threatened abortion?	☐	☐
13. Is the patient older than 35 years of age and does she smoke more than 10 cigarettes per day and have another risk factor for cardiovascular disease (e.g. diabetes mellitus, hyperlipidemia, hypertension, or family history of ischemic heart disease)?	☐	☐
14. Is the patient unlikely to understand or comply with the protocol requirements?	☐	☐
15. Will it take the patient more than one (1) hour to reach the source of emergency medical care that serves the abortion center from her home or place of work?	☐	☐
16. Will it take the patient more than one (1) hour to reach the source of emergency medical care from the abortion center?	☐	☐
Does the patient qualify for enrollment in the study?	☐	☐

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
1	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

DEMOGRAPHIC DATA

DATE OF BIRTH

___/___/___
M D Y

RACE/ETHNICITY (check one)

☐ 1. African American ☐ 2. Caucasian ☐ 3. East Asian
☐ 4. Hispanic ☐ 5. Other: _____

MEDICAL HISTORY

Please indicate whether the patient has any history of medical problems/surgeries in the following areas. If YES, comment in the space provided. If additional space is required, please use the comments section below.

	(check one) No	Yes	
1. Eyes, Ears, Nose, Throat, Mouth, Neck	☐	☐	_____
2. Respiratory	☐	☐	_____
3. Gastrointestinal	☐	☐	_____
4. Hepatic	☐	☐	_____
5. Renal-Genitourinary	☐	☐	_____
6. Gynecological	☐	☐	_____ APPEARS THIS WAY ON ORIGINAL
7. Hematopoietic-Lymphatic	☐	☐	_____
8. Musculoskeletal	☐	☐	_____
9. Neurological	☐	☐	_____
10. Dermatologic	☐	☐	_____
11. Cardiovascular	☐	☐	_____
12. Allergies (list causative agent)	☐	☐	_____
13. Other (specify)	☐	☐	_____

Comments (refer by item number): _____

_____

_____

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS
1	___ ___	___ ___ ___	___ ___ ___

PATIENT QUESTIONNAIRE

Please describe your marital status:

☐ Married Living With Partner ☐ Unmarried Living with Partner ☐ Living Without Partner

Number of years of schooling completed: ___ ___

What made you believe that you were pregnant?

_____ _____ _____

How long before you came to the clinic did you first suspect that you were pregnant?

☐ Within 1 Week ☐ 3-4 Weeks ☐ Over 8 Weeks

☐ 1-2 Weeks ☐ 5-8 Weeks

(circle one)

When you became pregnant, were you using anything to avoid pregnancy? No Yes

If yes, what were you using? _____

Other than the staff at the clinic, does anyone know about your pregnancy? No Yes

Other than the staff at the clinic, does anyone know about your decision to terminate your pregnancy? No Yes

Other than the staff at the clinic, is there a person supportive of your decision to terminate your pregnancy? No Yes

If you had elected to have a surgical abortion, what form of payment would have been used? (check all that apply)

☐ self pay ☐ medical insurance/HMO ☐ medicaid ☐ Other financial assistance

Why have you chosen to use the 'drug' method of abortion offered in this study?

_____

_____

VISIT 1 | CENTER NUMBER ___ ___ | PATIENT NUMBER ___ ___ ___ | PATIENT INITIALS ___ ___ ___ | DATE ___/___/___ (M D Y)

OBSTETRICAL HISTORY

Is this the patient's first pregnancy? (circle) Yes No (complete below)

How many children has the patient delivered? [ ][ ]

How many elective abortions has the patient had? [ ][ ]

How many miscarriages or spontaneous abortions has the patient had? [ ][ ]

What was the outcome of the patient's last pregnancy? (circle one)

1) live birth
2) still birth
3) spontaneous abortion
4) elective abortion
5) extrauterine pregnancy
6) molar pregnancy

When did the patient's last pregnancy terminate? ___/___/___ (M D Y)

DURATION OF PRESENT AMENORRHEA

Amenorrhea and gestational age are defined as the number of days beginning with the 1st day of the last menstrual period.

Date of Onset of Last Menses: ___/___/___ (M D Y) Number of days of amenorrhea: [ ][ ]

Transvaginal Ultrasound scan: Estimated gestational age [ ][ ] days

sac size: [ ][ ][ ] mm

crown rump length: [ ][ ][ ] mm

Pelvic Examination: Estimated gestational age [ ][ ] - [ ][ ] weeks

Final assessment of duration of amenorrhea: [ ][ ] days

Please check the appropriate group: (based on final assessment)

- ☐ Group 1=Amenorrhea of ≤ 49 days
- ☐ Group 2=Amenorrhea of 50 through 56 days
- ☐ Group 3=Amenorrhea of 57 through 63 days

LABORATORY STUDIES

Hemoglobin ___ ___ . ___ g/dL Hematocrit ___ ___ % Serum HCG ___ ___ ___ ___ ___ ___ IU/L

Blood typing (Rh status) ☐ Positive ☐ Negative Urine Pregnancy Test ☐ Positive ☐ Negative

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
1	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

PHYSICAL EXAMINATION

HEIGHT	WEIGHT	BLOOD PRESSURE	HEART RATE	TEMPERATURE
___ ___ ___ cm	___ ___ ___ kg	___ ___ ___/___ ___ ___ mmHg	___ ___ ___ BPM	___ ___.___ °C

	(check one) Normal	Abnormal	If Abnormal, briefly comment:
HEENT	☐	☐	_____
Chest/Lungs	☐	☐	_____
Cardiovascular	☐	☐	_____
Abdomen	☐	☐	_____
Skin	☐	☐	_____
Extremities	☐	☐	_____
Lymphatic	☐	☐	_____
Musculoskeletal	☐	☐	_____
Other _____	☐	☐	_____

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PELVIC EXAMINATION

	(circle)		(circle)
Fibroids	No Yes	Pelvic Inflammatory Disease	No Yes
Bleeding From Cervix	No Yes	Cervicitis	No Yes
Adnexal Masses	No Yes	Vulvo-Vaginitis	No Yes
Adnexal Tenderness	No Yes		

Comments: _____

_____

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
1	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

MIFEPRISTONE ADMINISTRATION

Date and time of last intake of solid food: ___/___/___ M D Y ___ ___:___ ___ (24 hour clock)

Date and time of mifepristone administration: ___/___/___ M D Y ___ ___:___ ___ (24 hour clock)

Lot number: JMP25524-109 Expiration date: July 1997

Clinic personnel supervising drug administration: _____ (PRINT)

☐ MD ☐ RN ☐ Counsellor

☐ PA ☐ CNM ☐ NP

Clinic personnel administering mifepristone: _____ (PRINT)

☐ MD ☐ RN ☐ Counsellor

☐ PA ☐ CNM ☐ NP

Patient diary should be dispensed and return visit scheduled for Study Day 3.

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
2	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

PATIENT STATUS

BLOOD PRESSURE	HEART RATE	TEMPERATURE
___ ___ ___/___ ___ ___ mmHg	___ ___ ___ BPM	___ ___.___ °C

Did the patient report any symptoms since Visit 1? (circle one)
No
Yes (record on page 12)

Did the patient use any concomitant medications since Visit 1?
No
Yes (record on page 13)

Review patient diary for adverse events and medication use.

ABORTION STATUS

Does the patient believe that expulsion occurred since the last visit? (circle one)
No (go to page 7)
Unsure (complete below)
Yes (complete below)

Date of expulsion: ___/___/___ (M D Y) Time of expulsion: ___:___ (24 hour clock)

Was the abortion ☐ complete ☐ incomplete ☐ ongoing pregnancy ☐ uncertain?

Abortion status was confirmed by: ☐ pelvic examination ☐ transvaginal ultrasound

*If abortion was **complete**, no misoprostol will be administered. Check appropriate box on page 7 (misoprostol not administered) and schedule return visit for Day 15.*

*If abortion was **incomplete or uncertain**, administer misoprostol and begin 4 hour monitoring.*

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
2	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

MISOPROSTOL ADMINISTRATION

Date and time of last intake of solid food: ___/___/___ M D Y ___ ___:___ ___ (24 hour clock)

If indicated, administer anti-RhD.

Date and time of anti-RhD administration: ___/___/___ M D Y ___ ___:___ ___ (24 hour clock)

☐ Not Administered

Date and time of misoprostol administration: ___/___/___ M D Y ___ ___:___ ___ (24 hour clock)

☐ Not Administered (specify reason)

_____

_____

Lot number: ☐☐☐☐☐☐ Expiration date: ___/___ M Y

Clinic personnel supervising drug administration: _____ (PRINT)

☐ MD ☐ RN ☐ Counsellor

☐ PA ☐ CNM ☐ NP

Clinic personnel administering misoprostol: _____ (PRINT)

☐ MD ☐ RN ☐ Counsellor

☐ PA ☐ CNM ☐ NP

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
2	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

POST-MISOPROSTOL OBSERVATION PERIOD

1. Record blood pressure, heart rate, nausea, vomiting, diarrhea and abdominal pain observed during the observation period below:

Time	Clock Time	Blood Pressure	Heart Rate
0	:	/	
1 hr	:	/	

Time	Clock Time	Blood Pressure	Heart Rate
2 hr	:	/	
3 hr	:	/	
4 hr	:	/	

Symptom	Start Time	Stop Time	Severity (Circle one item each line)
Nausea	:	:	0=None 1=Mild 2=Moderate 3=Severe
Vomiting	:	:	0=None 1=Mild 2=Moderate 3=Severe
Diarrhea	:	:	0=None 1=Mild 2=Moderate 3=Severe
Abdominal Pain	:	:	0=None 1=Mild 2=Moderate 3=Severe

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Record any medications given during the monitoring period on page 13.

Record adverse events other than nausea, vomiting, diarrhea and abdominal pain on page 12.

2. Time of expulsion __ __:__ __ (24 hour clock) ☐ no expulsion observed

3. Was the abortion ☐ complete ☐ incomplete ☐ ongoing pregnancy ☐ uncertain?

   Abortion status was confirmed by: ☐ pelvic examination ☐ transvaginal ultrasound

4. Did the patient require additional monitoring beyond the 4 hour observation period? (circle one) No / Yes (complete page 8.1)

5. Time patient discharged from clinic __ __:__ __ (24 hour clock)

Schedule return visit for study day 15.

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
2	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

POST-MISOPROSTOL OBSERVATION PERIOD EXTENDED MONITORING

1. Why was extended monitoring indicated for this patient?

☐ Cardiovascular events (specify): _____

Was an ECG conducted? ☐ No
☐ Yes (note results/diagnosis and attach a copy of tracing)

_____

☐ Heavy bleeding
☐ Abdominal pain
☐ Other (specify): _____

2. Record blood pressure, heart rate, nausea, vomiting, diarrhea and abdominal pain observed during the observation period below:

Clock Time	Blood Pressure	Heart Rate
:	/	
:	/	
:	/	
:	/	

Clock Time	Blood Pressure	Heart Rate
:	/	
:	/	
:	/	
:	/	

Symptom	Start Time	Stop Time	Severity
Nausea	:	:	0=None 1=Mild 2=Moderate 3=Severe
Vomiting	:	:	0=None 1=Mild 2=Moderate 3=Severe
Diarrhea	:	:	0=None 1=Mild 2=Moderate 3=Severe
Abdominal Pain	:	:	0=None 1=Mild 2=Moderate 3=Severe

Record any medications given during the monitoring period on page 13.

Record adverse events other than nausea, vomiting, diarrhea and abdominal pain on page 12.

VISIT	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
3	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

PATIENT STATUS

BLOOD PRESSURE	HEART RATE	TEMPERATURE	SERUM HCG
___ ___ ___/___ ___ ___ mmHg	___ ___ ___ BPM	___ ___.___ °C	___ ___ ___ ___ ___ ___ IU/L

HCT	HgB
___ ___ %	___ ___ g/dL

Did the patient report any symptoms since Visit 2? (circle one)
No
Yes (record on page 12)

Did the patient use any concomitant medications since Visit 2? (circle one)
No
Yes (record on page 13)

Review patient diary for adverse events and medication use.

APPEARS THIS WAY ON ORIGINAL

ABORTION STATUS

Does the patient believe that expulsion occurred after Visit 2 and prior to Visit 3? (circle one)
No (go to page 10)
Unsure (complete below)
Yes (complete below)

Date of expulsion: ___/___/___ (M D Y) Time of expulsion: ___ ___:___ ___ (24 hour clock)

APPEARS THIS WAY ON ORIGINAL

VISIT 3 | CENTER NUMBER ___ ___ | PATIENT NUMBER ___ ___ ___ | PATIENT INITIALS ___ ___ ___ | DATE ___/___/___ (M D Y)

PELVIC EXAMINATION

	(circle)		(circle)
Fibroids	No Yes	Pelvic Inflammatory Disease	No Yes
Adnexal Masses	No Yes	Cervicitis	No Yes
Adnexal Tenderness	No Yes	Vulvo-Vaginitis	No Yes

Status of Cervix: ☐ open ☐ closed

Comments: _____

_____

Abortion Status: ☐ complete abortion ☐ incomplete abortion ☐ ongoing pregnancy

Confirmed by: ☐ pelvic examination ☐ transvaginal ultrasound

☐ products of conception removed from vagina/cervix

If patient clearly has an incomplete abortion or ongoing pregnancy, conduct surgical abortion, and complete page 11.
If abortion was complete or probably complete, conduct exit interview.
If uterine bleeding is continuing, conduct exit interview and schedule follow-up.

APPEARS THIS WAY ON ORIGINAL

BLEEDING STATUS

Was medical intervention required to stop uterine bleeding? (circle one) No Yes

If yes: ☐ D&C ☐ hormonal therapy ☐ manual vacuum aspiration ☐ electric vacuum aspiration

Date of cessation of uterine bleeding: ___/___/___ (M D Y)
(check against patient diary)

CENTER NUMBER PATIENT NUMBER PATIENT INITIALS

____ ____ ____ ____ ____ ____ ____ ____

SURGICAL ABORTION

☐ Not conducted. Date of surgical abortion: ____/____/____ (M D Y)

Abortion method: ☐electric vacuum aspiration ☐sharp curettage ☐manual vacuum aspiration

Anesthesia method: ☐local ☐general ☐conscious sedation ☐none

Pathological description of aborted tissue (attach report): _____

_____

Schedule patient post-surgical follow-up visit.

POST SURGICAL ABORTION: PATIENT STATUS

☐ Clinic visit: ____/____/____ (M D Y) ☐ Telephone interview: ____/____/____ (M D Y)

Complete vital signs below.

BLOOD PRESSURE	HEART RATE	TEMPERATURE
_____/_____ mmHg	_____ BPM	____.___ °C

Did the patient report any adverse events since surgical abortion? (circle one) No / Yes (record on page 13)

CENTER NUMBER ____-____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

PATIENT QUESTIONNAIRE

Do you feel that the 'drug' abortion and side effects were adequately explained to you at the beginning of the study? (circle one) No Yes

If no, what could have been better explained? _____

_____

_____

When you were told that the 'drug' method of abortion required three visits to the clinic, was this difficult to schedule? No Yes

If yes, why? _____

_____

_____

Was your abortion experience similar to what you thought would happen? No Yes

If no, was the experience ☐ better or ☐ worse than expected?

Where were you when you had the abortion?

☐ at the clinic ☐ going to/coming from the clinic ☐ not sure/do not know
☐ at home ☐ elsewhere

Was there any problem with the timing or place of the abortion? No Yes

Was the duration of bleeding longer, shorter or about what you expected?

☐ longer ☐ shorter ☐ as expected ☐ not sure/do not know

Was the amount of blood flow more, less or about what you expected?

☐ more ☐ less ☐ as expected ☐ not sure/do not know

Was the abortion more painful, less painful or about as painful as you expected?

☐ more painful ☐ less painful ☐ as expected ☐ not sure/do not know

11.1

CENTER NUMBER ____ - ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

PATIENT QUESTIONNAIRE

How satisfactory was this abortion procedure?

☐ very satisfactory ☐ moderately satisfactory ☐ fair ☐ moderately unsatisfactory ☐ very unsatisfactory

Was your experience more satisfactory, less satisfactory or just as satisfactory as previous abortion experiences?

☐ more satisfactory ☐ less satisfactory ☐ just as satisfactory ☐ no previous abortion

What method was used to perform your last abortion?

☐ suction ☐ D & C ☐ other ☐ no previous abortion

What are the best features of this 'drug' method of abortion? _____

_____

_____

What are the worst features of this 'drug' method of abortion? _____

_____

_____

	(circle one) No	Yes
Would you feel comfortable taking the first medication at home?	No	Yes
Would you feel comfortable taking the second medication at home?	No	Yes
Based on your experience with the abortion procedure that you just used, would you choose the same procedure if you were considering abortion again?	No	Yes
Would you recommend this method of abortion to a friend or relative?	No	Yes

11.2

CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

ADVERSE EVENTS

(check one) No ☐ Yes ☐

Were any adverse events reported by the patient during the study?

Include any changes in symptoms, signs, or laboratory values including intercurrent illnesses and exacerbations of pre-existing conditions.

Severity:
1 = Mild
2 = Moderate
3 = Severe

Action Taken:
1 = None
2 = Drug Therapy*
3 = Hospitalization

Study Drug Related:
1 = Not related
Mifepristone 2 = Possible 3 = Probable
Misoprostol 4 = Possible 5 = Probable
Combination 6 = Possible 7 = Probable

Outcome:
1 = Recovered
2 = Improved
3 = Unchanged
4 = Worse
5 = Death

Description	Start Date	Stop Date (Circle "C" if continuing)	Severity	Action Taken	Study Drug-Related	Outcome
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				
	/ /	C / /				

*If treated with a concomitant drug, complete concomitant medications page.

CONCOMITANT MEDICATIONS

(check one) No ☐ Yes ☐

Were any concomitant medications taken by the patient during the study?
If **YES,** specify below:

Medication	Dosage	*Frequency	**Route	Date Started (M/D/Y)	Date Stopped (M/D/Y) (Circle "C" if continuing)	Indication
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	
				/ /	/ / C	

*Frequency: QD, BID, TID, QID, QOD, PRN
**Route: 1 = p.o.; 2 = s.c.; 3 = i.m.; 4 = i.v.; 5 = rectal; 6 = topical; 7 = nasal; 8 = inhaled; 9 = s.l.; 0 = other

CENTER NUMBER ____ ____ PATIENT NUMBER ____ ____ ____ PATIENT INITIALS ____ ____ ____

INVESTIGATOR'S QUESTIONNAIRE

PATIENT STATUS

1. Did the patient... (circle one)

   1. Complete the study?

   2. Withdraw before misoprostol? Date withdrawn: ____/____/____ (M D Y)

   3. Withdraw after misoprostol? Date withdrawn: ____/____/____ (M D Y)

   4. Become lost to follow-up before misoprostol? Date of last contact: ____/____/____ (M D Y)

   5. Become lost to follow-up after misoprostol? Date of last contact: ____/____/____ (M D Y)

APPEARS THIS WAY ON ORIGINAL

Comments: _____

_____

(circle one)

2. Given the clinical course of this patient, in the judgment of the investigator would No Yes

Comments: _____

_____

3. Given the clinical course of this patient, in the judgment of the investigator would No Yes

Comments: _____

_____

I have reviewed the complete case report form for this patient and find the data reported to be complete and accurate.

_____ ____/____/____

Principal Investigator Signature (M D Y)

	CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
UNSCHEDULED VISIT	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

PATIENT STATUS

BLOOD PRESSURE	HEART RATE	TEMPERATURE
___ ___ ___/___ ___ ___ mmHg	___ ___ ___ BPM	___ ___.___°C

(circle one)

Did the patient report any symptoms since the last visit? No / Yes (record on page 12)

Did the patient use any concomitant medications since the last visit? No / Yes (record on page 13)

Review patient diary for adverse events and medication use.

APPEARS THIS WAY ON ORIGINAL

Reason for clinic/office visit:

- ☐ Pain
- ☐ Bleeding
- ☐ Nausea
- ☐ Other medical problem
- ☐ Dissatisfaction with duration of abortion process
- ☐ Uncertainty about abortion
- ☐ Other

Result of visit:

- ☐ Patient requests surgical abortion (complete pages 11-14).
- ☐ Elective surgical abortion suggested by physician (complete pages 11-14).
- ☐ Surgical abortion indicated by patient's condition (complete pages 11-14).
- ☐ Ongoing medical abortion, no intervention.

ABORTION STATUS

(circle one)

Does the patient believe that expulsion occurred since the last visit? No / Uncertain (complete below) / Yes (complete below)

Date of expulsion: ___/___/___ (M D Y) Time of expulsion ___:___ (24 hour clock)

Was the abortion ☐ complete ☐ incomplete ☐ ongoing pregnancy ☐ uncertain?

Abortion status was confirmed by: ☐ vaginal examination ☐ transvaginal ultrasound

___.1

CENTER NUMBER	PATIENT NUMBER	PATIENT INITIALS	DATE
UNSCHEDULED VISIT	___ ___	___ ___ ___	___ ___ ___	___/___/___ M D Y

EXAMINATIONS/PROCEDURES CONDUCTED
(check all that apply)

☐ Physical Examination
- ☐ Normal
- ☐ Abnormal Findings: _____

☐ Pelvic Examination
- ☐ Ongoing Pregnancy
- ☐ Incomplete Abortion
- ☐ No Pregnancy
- ☐ Other: _____

☐ Ultrasound Examination
- ☐ Ongoing Pregnancy
- ☐ Incomplete Abortion
- ☐ No Pregnancy
- ☐ Not Done
- ☐ Other: _____

☐ Laboratory Tests
- ☐ Hemoglobin ___ ___ g/dL
- ☐ Hematocrit ___ ___ %
- ☐ Other blood/serum analysis (attach reports)
- ☐ Other (attach reports): _____

☐ Please attach pathology report for any surgical abortion procedures.

☐ Other (describe/attach pertinent reports on any procedures conducted)

_____

_____

___.2

ILLNESSES/SYMPTOMS

Date	Illness/Symptom	Time Started	Time Stopped	Severity
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe
		AM PM	AM PM	Mild Moderate Severe

PROTOCOL 166A/B

CENTER NUMBER ☐☐ PATIENT NUMBER ☐☐☐ PATIENT INITIALS ☐☐☐

Thank you for participating in this clinical trial. Inside you will find a chart to register your menstrual symptoms and space to record medications used during the study. On the back, please list any illnesses/adverse events which occur during the course of the study.

CLINIC VISIT SCHEDULE

Visit 2 ____/____/____ (M D Y) Visit 3 ____/____/____ (M D Y) Additional Visits ____/____/____ (M D Y) ____/____/____ (M D Y)

IF YOU NEED EMERGENCY CARE DURING THE STUDY, CALL *(days)* _____
(evenings, weekends) _____

Call one of these numbers if you have heavy menstrual bleeding, fever, severe abdominal pain or other medical problems.

SUBJECT'S DIARY

MENSTRUAL SYMPTOMS

Mark an 'X' in the appropriate box for each symptom which occurs during the study.

STUDY DAY	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Date															
Heavy Bleeding															
Normal Bleeding															
Spotting															
Pain/Cramps															
Abortion/Expulsion															

*Day 1 is the day of taking mifepristone.

MEDICATION USE

Medication	Total Daily Dose	Date Started	Date Stopped (circle C if continuing)	Reason for Use
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	
		/ /	/ / C	

CENTER NUMBER ____ ____ SCREENING NUMBER ____ ____ ____ DATE ____/____/____ M D Y

NON-PARTICIPANT PATIENT QUESTIONNAIRE

Complete for all patients who are offered the possibility of trying the medical abortion method and are not excluded by study criteria but decline to participate at any point prior to signing an informed consent.

We are trying to find out something about the reasons that women would prefer not to use a medical abortion method. Would you mind answering 5 quick questions? Neither your name nor any way of identifying you will appear with this information.

Age: _____

Ethnicity/Race:

☐ African American ☐ Hispanic/Latina ☐ Other: _____
☐ East Asian ☐ White

Social Circumstances:

☐ Married, living with partner ☐ Unmarried, living with partner ☐ living without partner

Have you had an induced abortion before today?

☐ Yes ☐ No

Why did you choose not to try a medical abortion method? (Do not prompt patient, check all that apply)

☐ Did not want to be in a study.
☐ Afraid of new drug/experiment.
☐ Method requires too many visits.
☐ Afraid of a lot of/long bleeding.
☐ Afraid of pain.
☐ Afraid to see embryo.
☐ Method fails too often.
☐ Want quicker result/procedure.
☐ Other (specify): _____

Continuation of Protocol 166B

Appendix C

Part E. Publications Based on the Study

B.Protocol Cover Sheet

APPENDIX C
ROUSSEL LABORATORIES PROTOCOL FFR/91/486/14
PROTOCOL COVER SHEET

Study Phase: III

Name of Drug: Mifepristone
Active Ingredient: Mifepristone
Dosage: 600 mg
Route of Administration: Oral
Duration of Treatment: Single Dose

Objective: To evaluate the efficacy, tolerance and safety of 600 mg mifepristone followed by 0.4 mg misoprostol 48 hours later for the termination of pregnancy in women whose duration of amenorrhea was no more than 49 days.

Patient Population: Women aged 18-35 who were ≤49 days from onset of their last menstrual period and who requested a voluntary termination of pregnancy.

Structure: Single Group
Multicenter: Yes
Number of Centers: 24
Common Training: Yes
Blinding: None
Method of Patient Assignment: All patients were assigned to treatment with 600 mg mifepristone and 0.4 mg misoprostol

Concurrent Control: None

Estimated Total Sample Size: 1000
Statistical Rationale Provided: No

Primary Efficacy Variable: Proportion of patients with complete expulsion of the products of conception.

Adverse Reactions: Volunteered

Plan for Data Analysis: No

C.Protocol with Amendment and Case Report Form (English Translation)

(Original Language Document is located in Appendix D1)

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ON ORIGINAL

ROUSSEL Laboratories
Medical Division

Protocol FFR/91/486/14

EFFICACY AND SAFETY OF MIFEPRISTONE (RU 486) AT THE DOSE OF 600 MG IN A SINGLE ADMINISTRATION IN COMBINATION WITH MISOPROSTOL AS AN ALTERNATIVE TO UTERINE ASPIRATION FOR INTERRUPTION OF PREGNANCIES AGED LESS THAN OR EQUAL TO 49 DAYS OF AMENORRHEA

May 1991

Medical Coordinators:	Dr. Remi PEYRON ROUSSEL Laboratories 97, rue de Vaugirard 75006 PARIS Tel. (1) 40 62 41 40 Dr. Louise SILVESTRE ROUSSEL ICLAF 102, rue de Noisy 93230 ROMAINVILLE Tel. (1) 48 91 46 60
Clinical Research Associates:	Dr. Veronique TARGOSZ ROUSSEL Laboratories 97, rue de Vaugirard 75006 PARIS Tel. (1) 40 62 44 57 ROUSSEL UCLAF 102, route de Noisy 93230 PARIS Tel [redacted]
Head of Information n Mifégyne:	[redacted] Tel. [redacted]
Pharmacovigilance:	[redacted] ROUSSEL Laboratories 97, rue de Vaugirard 75006 PARIS Tel. [redacted]
Biometry:	[redacted] Tel. [redacted]
Proper Clinical Practice and Quality Control:	[redacted] ROUSSEL Laboratories 97, rue de Vaugirard 75005 PARIS Tel [redacted]
Coordinating Researcher:	Dr. Elisabeth AUBENY Orthogenics Center BROUSSAIS Hospital 96, rue Didot 75014 PARIS Tel. (1) 43 95 95 95

LIST OF INVESTIGATORS

MIFEPRISTONE-MISOPROSTOL PROTOCOL - No. FFR/91/486/14

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Dr. CHARLES Francois	Sce. Obstetrics de l'Quest	Route de Marseille	83190 OLLIOULLES	94 27 91 50 94 88 94 48
Dr. DEQUIDT - Dr. RETTEL	Hospital N.D. de Bon Secours - Sce Gyne.	1, pl. de Vigneulles B.P. 1065	57038 METZ Cedex	87 55 31 31
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Dr. MISSEY KOLB Heliane	C.H. - Orthogenics Center	4, rue Baronne Gerard	78104 ST GERMAN en LAYE	39 73 92 01
Dr. NENY	Hopital BRETONNEAU - Centre d'Orthogenie	2, bd Tonelle	37044 TOURS Cedex	49 47 47 47
Dr. PIDOUX	C.H.G. - Sce Gynco-Obstetrique	Rue de Kersaint Gilly B.P. 237	29205 MORLAIX	98 62 61 60
Dr. PLATEAUX	Hopital BICETRE - Centre d'orthogenie	78, rue General Leclerc	94275 Kremlin Bicetre Cedex	45 21 27 28

LIST OF INVESTIGATORS continued

Dr. GEFFROY (mme le)	C.H.G. - Centre d'I.V.G.		44606 St. NAZAIRE	40 90 60 60
Dr. SCHARFMAN	Hopital de la Fraternite	20, ave Julien Lagache B.P. 359	59056 ROUBAIX Cedex	20 99 32 30 (cabinet) 20 54 31 33
Dr. SERFATY - Dr. DREYFUS	Hopital Saint Louis - Centre d'Orthogenie	2, pl de Dr. A. Fournier	75010 PARIS	42 49 49 49
Dr. VAN DEN BOSSCHE / Dr. JOURDAN	Hopital Jean DUCOING - Centre d'Orthogenie	15, rue de Varsovie	31000 TOULOUSE	61 77 34 00
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Dr. VITANI	HOTEL DIEU Hopital de la Croix Rousse-Centre d'Orthogenie	1, place de l'Hopital 93, Gde rue de la Croix Rousse	69002 LYON 69317 LYON CEDEX	78 92 20 00 78 29 87 33
Dr. WANG	Clinique de Montrouge	24, rue Perrier	92120 MONTROUGE	46 57 12 45 (cabiner) 45 86 79 00

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1. INTRODUCTION

Mifepristone (RU 486, Mifégyne®) is an anti-progesterone compound synthesized by ROUSSEL UCLAF. Prior studies have shown that it is capable by itself of interrupting approximately 80% of pregnancies aged less than or equal to 41 days of amenorrhea (DA) (1), when it is given at the dose of 600 mg orally in a single administration. Past that date, the efficacy of the product alone diminishes rapidly (drop of about 10% in the success rate per week of additional amenorrhea). Swedish (2), Scottish (3) and French (4-5) studies have shown that combining Mifepristone with a synthetic prostaglandin analog (Sulprostone or Gemeprost), completely interrupts the pregnancy in 95% of the cases, for amenorrhea up to 49. These studies also indicate that combining Mifepristone with prostaglandin lowers the useful doses of prostaglandin (0.25 mg for Sulprostone, 0.5 or 1.0 mg for Gemeprost), hence a reduction in their side effects.

The optimum time period between the administration of Mifepristone and the administration of prostaglandin is 36 to 48 hours. In fact, the cervical dilation caused by mifepristone is greater at 48 than at 24 hours, and the sensitivity of uterine muscle to the contractive effect of prostaglandins is maximum 36 to 48 hours after the administration of mifepristone (6.7).

Mifepristone has been registered in France as a medical alternative to uterine aspiration of pregnancy of no more than 49 days of amenorrhea; it is prescribed at the dose of 600 mg (three 200 mg tablets) in a single administration and is followed 36 to 48 hours later by the administration of 1 mg of Gemeprost ——— , or 0.25 mg of sulprostone ———

In one study of approximately 16,000 women (8), the safety for this method of interrupting pregnancy was acceptable. Within 4 hours following the administration of prostaglandin, painful uterine contractions occurred in approximately 80% of the women; these contractions necessitated treatment in 20% to 60% of the patients depending on the prostaglandin dose used (1 mg of gemeprost, 0.25 or 0.5 mg of sulprostone). During that same period, vomiting (15% of cases) and diarrhea (7.5% of cases) were observed. Faintness as a result of hypotension or lipothymia were also reported in approximately 1% of the cases.

The other adverse effects most often reported after that 4-hour period following the prostaglandin were painful uterine contractions (1.6%), headache (1%), gastrointestinal problems: nausea (0.8%), vomiting (0.5%), skin eruptions (0.2%) (8). Uterine bleeding necessitated a hemostatic endo-uterine procedure in 0.8% of the cases, and a transfusion in 0.1% of the cases.

Out of all the women who have used this method (approximately 60,000), three severe adverse effects of the myocardial infarction type have been reported, one of which was fatal. These infarctions seem to be connected with a coronary spasm and all of them occurred within 4 hours following the injection of sulprostone. The patients involved were all over 30 years of age and smoked. These coronary spasms are probably attributed to sulprostone and have also been described after isolated injection of sulprostone (9).

In view of these accidents, the decision was made to determine whether prostaglandins other than the ones previously studied could be combined with mifepristone.

Misoprostol is a synthetic derivative of the PGE_1 series (15-desoxy 16-hydroxy 16 methyl analog) administered orally at the dose of four 0.2 mg tablets 4 per day to treat ulcerous duodenal or gastric lesions (10).

This product is widely prescribed. At the dose of four 200 mg tablets per day, it causes no hypotension and its cardiovascular safety seems acceptable. No serious cardiovascular effect has been published to date, and the pharmacovigilance data are favorable (11).

This prostaglandin can stimulate the contraction of smooth muscle fibers, particularly uterine fibers. It is therefore contraindicated in its current indication in pregnant women or sexually active women who do not have an effective method of contraception.

One preliminary study in 100 women (12) has shown that prescribing 600 mg of mifepristone, followed 48 hours later by 2 tablets of misoprostol, enabled interruption and complete expulsion of 95% of pregnancies of no more than 49 days of amenorrhea. The method's safety was satisfactory. The main adverse effects were nausea (35 cases), vomiting (11 cases) and diarrhea (7 cases), which symptoms did not necessitate any treatment. Conversely, the intensity of the uterine pain seems to be definitely lower than with the prior prostaglandins used (sulprostone, gemeprost). The duration of bleeding did not change.

Therefore, considering all the above information, it seems worthwhile to confirm the efficacy and safety of this combination in a large-scale study.

2. PURPOSE OF THE STUDY

The purpose of this study is to evaluate the efficacy and safety of using Mifepristone (600 mg), in combination with two 0.2 mg tablets of misoprostol administered 48 hours later, for interruption of pregnancy aged less than or equal to 49 days of amenorrhea, within the framework of the law on voluntary interruption of pregnancy in France.

3. DESCRIPTION OF THE STUDY

This is an open, multicenter trial studying the following therapeutic plan:

- Mifepristone will be administered at the dose of 600 mg (three 200 mg tablets) in the presence of the researcher on day 1 after verification of the inclusion criteria.
- Misoprostol (two 0.2 mg tablets in a single administration) will be administered 48 hours later, the morning of day 3, also in the presence of the investigator. The women will be kept under observation in a hospital setting for 4 hours.

The efficacy and safety of the treatment will be evaluated 8 to 15 days after the administration of mifepristone in a follow-up visit.

4. CHOICE OF SUBJECTS

4.1 Number

The anticipated number of patients is 500. These patients will be recruited in 24 centers.

4.2 Inclusion Criteria

The following will qualify for inclusion: women who

- request interruption of pregnancy (I.V.G.*),
- meet the mandatory statutory requirements for I.V.G. in France,
- range in age from 18 (legal age of consent; underage women can be included only with the consent of their legal guardian) to 35 years of age,
- agree to submit to the constraints of the study, specifically the follow-up visit following administration of the treatment,
- are informed of the usual procedure for a miscarriage,
- agree to undergo an surgical interruption of pregnancy should the treatment fail,
- are informed of the procedure of the study and have given their written consent to participate in it (appendix 1),

and whose pregnancy is:

- intra-uterine,
- ongoing,
- of stated age less than or equal to 49 days of amenorrhea (calculated from the first day of the last menstruation).

(The occurrence of an IUD pregnancy is not a contraindication, provided that it is removed when mifepristone is administered).

4.3. Exclusion Criteria

The following will not qualify for inclusion: women who

- have signs of spontaneous miscarriage in progress,
- have a suspicion of extra-uterine pregnancy,

*[interruption volontaire de grossesse = voluntary interruption of pregnancy]

- whose amenorrhea is longer than 49 days,
- are more than 35 years of age,
- are smokers, defined as smoking at least 10 cigarettes per day for 2 years preceding the start of the study,
- have one of the following pathologies: cardiovascular history (angina pectoris, rhythm disorders, cardiac insufficiency, severe hypertension...), asthma, glaucoma or high intraocular pressure, diabetes, hyperlipemia.
- have renal, adrenal or hepatic insufficiency currently or in their histories,
- have been treated with corticoids chronically for the preceding six months,
- have a known allergy to mifepristone,
- have anemia,
- refuse to give their written consent to participate,
- who are thought to be prone to stray from the requirements of the protocol, or who live far from the center.

5. TREATMENT

5.1 Mifepristone

The Mifepristone will be supplied by the Roussel Laboratories in the form of 200 mg tablets of micronized active product. The tablets will be packed in 3-tablet blisters.

The product will be given in a single 3-tablet administration, in the presence of the invesitgator, on an empty stomach.

The boxes of mifepristone will be labeled as follows:

- Protocol number FFR 91/486/14
- Mifepristone - Misoprostol Study
- Roussel Laboratories
- Batch No. - Expiration date
- Patient No. (0001 to 0500)

All boxes of mifepristone needed by a center will be given to that center's head pharmacist, who will distribute them to the investigator.

After verifying the inclusion and exclusion criteria, the women will be assigned a study admission number and she will then be given the box bearing that number. The numbers will be assigned in order.

A record sheet of products under study must be kept up to date by the investigator.

At the end of the study, all unused products and the product record sheet must be collected by the clinical research assistant.

5.2. Prostaglandin Analog

The prostaglandin analog used will be misoprostol (Cytotec®). It will be administered 48 hours after the administration of mifepristone at the dose of two 0.2 mg tablets in a single administration, in the investigator's presence. The women will then be observed at the center for 4 hours.

The misoprostol will be supplied to the center's head physician by the Roussel Laboratories.

5.3 Combined Treatments

5.3.1 Authorized treatments

Insofar as possible, no other treatment will be combined. If a prescription is made, the type and dose of the medication will be indicated in the observation notebook.

Treatments in progress will be indicated in the observation notebook.

5.3.2 Prohibited Treatments

- Acetylsalicylic acid and derivatives thereof, steroidal or non-steroidal anti-inflammatories, prostaglandin synthesis-inhibiting medications (if necessary, an analgesic will be used that belongs to another pharmacological class or an antispasmodic in preference over one of these medications), enzyme-inducing medications.

- oxytocics or prostaglandins other than the one used in the study.

- The patient must refrain from self-medication.

- The patient must abstain from smoking or drinking alcohol during the 48 hours between the administration of mifepristone and misoprostol, and on the day the misoprostol is administered.

6. EVALUATION CRITERIA

6.1 Efficacy

Efficacy will be evaluated 8 to 15 days after administration of Mifepristone (day 8 - day 15) by the investigator, on clinical data (occurrence of bleeding, expulsion of ovular sac, persistence of bleeding), biological and/or ultrasound data.

A distinction will be made between:

1) Interruption and complete expulsion of pregnancy (disappearance of clinical signs, drop in beta HCG compared to day 1 and/or uterine vacuity, with no need for an additional surgical procedure (aside from possible forceps-aided extraction of ovular fragments protruding from the external orifice of the cervix). The date and time of the expulsion will be noted, if possible. This will be considered as a success.

2) Interruption of pregnancy without complete expulsion.

3) Persistent pregnancy.

4) The need for a hemostatic endo-uterine procedure.

Cases 2, 3 and 4 will be followed by additional surgical therapy, the date of which will be recorded. They will be considered failures.

6.2 Safety

6.2.1. When misoprostol is administered (day 3):

Safety will be evaluated on:

- Any adverse effect occurring between day 1 (administration of mifepristone) and day 3.
- Occurrence, within 4 hours of administering misoprostol, of painful uterine contractions and digestive problems: nausea, vomiting, diarrhea. The intensity of these symptoms will be noted along with any need for a symptomatic treatment.
- For 4 hours following administration of misoprostol, hourly observation of blood pressure (systolic and diastolic) and heart rate.
- Occurrence of an adverse effect other than the ones indicated above.

6.2.2 At Follow-Up Visit (day 8 - day 15):

Safety will be evaluated based upon:

- The duration of uterine bleeding and the need for special measurements: measurement of hemoglobin concentration, medication treatment, blood transfusion, hemostatic surgical procedure.

- Any unusal clinical sign or symptom that has occured since day 3.

6.2.3 Biological Safety

This will be evaluated based upon the hemoglobin rate measured on day 1 (before administering mifepristone) and on day 8 - day 15 at the time of the follow-up visit.

7.1 Initial Evaluation (day 1)

Verify that the patient has taken the legal measures to request a voluntary interruption of pregnancy and has met the conditions stipulated by the law (waiting period):

- Record:

· the main history,
· any treatments in progress and the reasons for them,
· the date of the last menstruation.

- Verify that the age of the pregnancy is less than or equal to 49 days of amenorrhea.

- Measure the bHCG and do a uterine ultrasound.

- Determine the Rhesus group if the patient has no group card, and measure the hemoglobin rate.

- Give the patient a data sheet on the study and obtain her written consent to participate in it.

- Assign the women a study admission number and give her the 3 tablets of mifepristone contained in the box bearing that number. The treatment will be taken immediately in the presence of the investigator. The number will be noted in the observation notebook.

- Inform the women that she must refrain from smoking and drinking alcohol for the next 48 hours and on day 3.

- Make an appointment for the morning two days later (day 3).

7.2. Day 3: Administration of Misoprostol:

- Clinical examination

- Look for any adverse effect.

- Give an injection of anti D gamma globulins if the patient is Rhesus negative.

- Administer two 0.2 mg tablets of misoprostol in a single administration (if expulsion has not already occurred) in the investigator's presence.

- The patient must remain under observation at the center for the next 4 hours.

- During these 4 hours of observation, the following parameters are evaluated:

· Painful uterine contractions, nausea, vomiting, diarrhea, using the following scale:

1: minimal
2: moderate
3: major, not necessitating treatment
4: major, necessitating treatment

* the overall intensity of the pain during this observation will also be evaluated on an analogous visual scale 4 hours after administration of misoprostol,

* if a premedication is given, it will be noted in the observation notebook,

* the treatments administered will be recorded in the observation notebook.

· Heart rate, systolic and diastolic blood pressure will be measured every hour.

- Note the time of ovular expulsion if it occurs during the time that the patient is under observation.

- If the patient has chest pains, a rhythm disorder or hypotension, an EKG must be done. In the event of severe pain, rapid-acting nitrate derivatives will be prescribed, in the hypothesis of a coronary spasm.

- After 4 hours, the woman is authorized to leave the center and is given an appointment for day 8 - day 15, with a prescription for a hemoglobin measurement just before the next visit.

- An oral contraceptive to be started 24 to 48 hours later can be prescribed during this visit.

7.3. Day 8 - Day 15: Follow-up Visit:

- New clinical examination and evaluation of safety by the investigator.

- If possible note the date of ovular expulsion and the time of expulsion with respect to the time of administration of prostaglandin.

- Final evaluation of efficacy of treatment (by the data from the clinical examination, bHCG and/or ultrasound).

- If the patient has started an oral contraceptive before this follow-up visit, note the name of the contraceptive prescribed.

- Evaluation of metrorrhagia:
  - duration,
  - was there any need for an emergency measurement of the hemoglobin concentration (note the result)?
  - was there any need for a treatment (medication, transfusion, hemostatic surgical procedure)?

- In the event of failure (ongoing pregnancy, incomplete expulsion), recommend an additional surgical procedure.

- Note the results of the hemoglobin measurement.

8. DATA COLLECTION AND ANALYSIS

8.1. Data collection:

An observation notebook will be filled out for each patient admitted to the study. Only the investigator and his/her colleagues are authorized to fill in the notebook or make any corrections in it.

Any correction in the observation notebook must be made by drawing a line through the incorrect data so that it remains visible, and putting the correct data alongside it. The person who made this correction must enter the date and put his/her initials in the margin. Each observation notebook must be signed and dated by the investigator.

8.2. Data analysis:

The data will be analyzed by the Biometry Department of the Roussel Laboratories. It will be primarily descriptive.

9. AMENDMENTS TO THE PROTOCOL

There can be no modifications in the protocol without Roussel's written consent.

Any modification must be the subject of an amendment documented and justified in writing. It must be signed by the investigator accepting the change in the study procedure.

This amendment in the protocol must be submitted and approved by the Ethics Committee if it is liable to modify the expected medical benefit/risk ratio for the patient, in a way unfavorable to the patient.

If the modification of the protocol is necessary immediately to assure patient safety, the persons in charge of the study will submit the amendment to the Ethics Committee after it is applied, but as soon as possible.

10. SIDE EFFECTS AND ADVERSE EVENTS

10.1. Serious Adverse Event:

A serious adverse event is defined as:

- any event entailing a fatality or undermining the life prognosis,

- any event leaving sequelae or developing in a chronic fashion,

- any event necessitating hospitalization or extension of hospitalization,

- discovery of a congenital anomaly or a cancer.

- an overdosage.

Any serious adverse event must be immediately reported to the Roussel laboratories:

- Dr. Remi Peyron	Tel. 1 40 62 41 40 Fax. 1 40 62 49 68

OR

- Dr. Louise Silvestre	Tel. 1 48 91 46 60 Fax. 1 48 91 49 49

A written confirmation must be sent in the form of the adverse effect record sheet (an example is in appendix 2) either by fax or by express mail.