NOV 30 1995 ORIGINAL

Pre-NDA
Mifepristone

Population Council
October 24, 1995

Memorandum of Meeting

Industry Patricipants:
Wayne Barden, M.D., Vice-President Population Council
Ann Robins, Ph.D., Staff Scientist, Population Council
[redacted] Consultant
Ms. Karon Walker, Population Council

FDA Staff:
[redacted] (HFD-713)
[redacted] (HFD-426)

Background:
The Division requested this meeting to discuss the mechanics of the NDA submission which the sponsor is planning to submit before the end of the year.

Discussion and Conclusion:
Dr. Bardin outlined the status of the US trials, and the contractual status of the drug substance manufacturer, and drug product manufacturer. He stated that Gideon Richter (GR) has signed a contract to supply drug substance, and has resolved their synthesis problems; Roussel Uclaf (RU) has given GR the manufacturing data they require. The contract with an unnamed drug product manufacturer is not yet signed but it is expected to be soon.

Dr. Bardin then described the organization and content of the NDA (see attached). He noted that the human pharmacokinetics data/bioavailability data were submitted to the IND [redacted] (serial number 103) in September 1994. [redacted] told the sponsor that she never received the submitted pharmacokinetic data, therefore, she could not make any comments regarding the quality of such information. [redacted] also mentioned that if the sponsor is planning to support their NDA-pharmacokinetic section mainly on published reverences, then the sponsor needs to organize and summarize the published literature according to the Division of Biopharmaceutics requirements and a copy of each cited reference should be included. [redacted] gave the firm a copy of the Biopharmaceutic Guidelines on how the pharmacokinetic section should be organized and what information should be included.

Dr. Bardin noted that the chemistry section will be submitted by RU directly to the IND, in the required NDA format, this month. He stated that RU had refused to submit the information either directly to the NDA or as a Drug Master File because of their reluctance to be seen as having anything to do with obtaining approval for this drug in the U.S. Dr. Bardin also said that two letters specifying the agreements that RU has made regarding submission of information had been recently finalized. A copy of both of those letters will be submitted within the week.

[redacted] told the sponsor that we were not certain we could legally accept a cross-reference to an IND for the CMC section of an NDA. This Division will consult with [redacted] of the general counsel's office regarding this. [redacted] also stated that this Division will be

contacting RU to discuss their portion of the submission in order to be certain that the NDA will be complete upon submission, Dr. Bardin will submit a contact person with RU to facilitate this.

Dr. Bardin said that the French trials which will be submitted have been audited and reanalyzed by the Population Council; any discrepancies will be noted and explained. The discrepancies are described as a patient added or not counted by the French investigators for whatever reason. All discrepancies are said to be minor.

Finally Dr. Bardin presented an overview of the proposed chemistry supplement to the hoped for approved NDA, and the efficacy supplement. The chemistry supplement will bring GR and the as yet unnamed drug product manufacturer into the NDA. Until this happens, no drug product will be marketed in the U.S. The efficacy supplement will contain all of the U.S. trial data and information from the French pivotal trials to support an extension of the drug use period to sixty days.

Action Items:
Dr. Bardin will submit within the week a copy of both letters of agreement between RU and the Population Council regarding the information which RU will submit on the Population Councils behalf for the CMC section of the NDA. Once those letters are received, a meeting with ——— of Office of General Council will be held to determine whether the CMC data can be submitted to an IND. Dr. Bardin will also submit a name and number of a regulatory person to contact for a CMC teleconference between the chemists of this Division and RU in order to discuss RU's submission.

/S/ 11/30/95
———
CSO

cc:
IND ———
HFD-510
MEETING ATTENDEES
HFD-870/ ———
HFD-713/ ———
HFD-510/ ———
HFD-510/ ———/10.25.95/ ———
concurrences: ——— 10.26.95/ ——— 10.26.95/ ——— 10.27.95/ ——— 10.31.95 ———
11.1.95/ ——— 11.1.95/ ——— 11.2.95/ ——— 11.2.95/ ———
11.6.95 ——— 11.16.95

MEETING MINUTES

N-154

[redacted]

The Population Council
Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

November 2, 1995

ORIGINAL

By FedEx

Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Attn: Document Control Room 14B-03
Food and Drug Administration
560 Fishers Lane
Rockville, MD 20857

Subject: IND [redacted] Mifepristone Tablets, 200 mg
Submission Serial Number: 154
IND Safety Report

Dear [redacted]

Enclosed please find an FDA form 3500 regarding an adverse event reported to the Population Council for the above referenced study. This event occurred [redacted] at that site.

Please contact me should there be any questions or comments regarding the above information.

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin

Enclosure

CWB/ar

The Population Council
Center for Biomedical Research
1230 York Avenue
New York, NY 10021

Telephone: 212-327-8731
Facsimile: 212-327-7678

ORIGINAL
N 158
JC

VIA FEDERAL EXPRESS

March 8, 1996

[redacted], Division of Metabolism
and Endocrine Drug Products
HFD-510
Center for Drug Evaluation and Research
Document Control Room - 14B-03
Food and Drug Administration,
5600 Fishers Lane
Rockville, MD 20857

Subject: IND [redacted] Mifepristone Tablets, 200 mg
Submission Serial Number: 158
Information Amendment - Chemistry

Dear [redacted]

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our IND with additional information on the Chemistry, Manufacturing and Control data for mifepristone. This information extends and completes the information which was submitted on 27 October, 1995 in Submission Serial No. 135.

The following data are presented in the attached appendices, as indicated below:

Appendix I: Environmental Assessment

Appendix II: Statement regarding the investigational formulation

Appendix III: A copy of the information which will be submitted in the [redacted] Methods Validation Section of the mifepristone NDA

Appendix IV: Additional information regarding the synthesis of mifepristone

In addition, I wish to confirm that our third party manufacturer is willing to undergo establishment inspections, should this be needed. If there are any further questions related to this CMC information, do not hesitate to contact me directly at 212-327-8748.

Best regards,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

ORIGINAL

The Population Council
Center for Biomedical Research
1230 York Avenue
New York, NY 10021

/S/ Telephone: 212-327-8731
Facsimile: 212-327-7678

VIA FEDERAL EXPRESS

March 15, 1996

[redacted] Division of Metabolism
and Endocrine Drug Products
HFD-510
Center for Drug Evaluation and Research
Document Control Room - 14B-03
Food and Drug Administration,
5600 Fishers Lane
Rockville, MD 20857

Subject: IND [redacted] Mifepristone Tablets, 200 mg
Submission Serial Number: 159
Information Amendment - Chemistry
- Clinical

Dear [redacted]

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our IND with additional information on chemistry and clinical data related to the use of mifepristone.

Appendix I contains a 12 month stability report on mifepristone tablets (200 mg) used in U.S. clinical trials 166A and 166B.

Appendix II contains a periodic safety update report on mifepristone received from Roussel Uclaf, which covers safety information reported to this company from June 1, 1995 to November 30, 1995, and Roussel Uclaf's quarterly safety line listing which covers the period of October 1, 1995 through December 31, 1995.

Appendices III and IV contain copies of the Investigators' Brochure for mifepristone prepared by Roussel Uclaf for use in France and Canada, respectively.

Appendices V through X contain several study reports on clinical studies of mifepristone received from Roussel Uclaf. Full study reports are enclosed, with the exception of two studies for which only the synopsis is included here, since the full report is available in Mifepristone NDA No. 20,687, submitted March 14, 1996. However, upon request, the Population Council will submit the full reports of these two studies to this IND.

Sincerely,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPENDIX A.1

PROTOCOL

APPEARS THIS WAY
ON ORIGINAL

LABORATOIRES ROUSSEL
DIRECTION MEDICALE

PROTOCOL FFR/91/486/14

EFFICACY AND TOLERANCE OF MIFEPRISTONE (RU 38486) IN A SINGLE DOSE OF 600 MG IN COMBINATION WITH MISOPROSTOL AS AN ALTERNATIVE TO UTERINE ASPIRATION FOR THE TERMINATION OF PREGNANCIES OF LESS THAN OR EQUAL TO 49 DAYS OF AMENORRHOEA

MAY 1991

Medical co-ordinators:	Rémi PEYRON, M.D. Laboratoires ROUSSEL 97, rue de Vaugirard 75006 PARIS Tel. (1) 40 62 41 40 Louise SILVESTRE, M.D. Roussel Uclaf 102, route de Noisy 93230 ROMAINVILLE Tel. (1) 49 91 46 60
Clinical Research Assistants:	Véronique TARGOSZ, M.D. Laboratoires ROUSSEL 97, rue de Vaugirard 75006 PARIS Tel. (1) 40 62 44 57 [redacted] Roussel Uclaf 102, route de Noisy 93230 ROMAINVILLE Tel. (1) 49 91 54 20
Responsible for Information about Mifegyne:	[redacted] Tel. 88 75 64 76
Pharmacovigilance:	[redacted] Laboratoires ROUSSEL 97, rue de Vaugirard 75006 PARIS Tel. (1) 40 62 48 65
Biometry:	[redacted] Tel. (1) 40 62 40 23
Good Clinical Practice and Quality Assurance:	[redacted] Laboratoires ROUSSEL 97, rue de Vaugirard 75006 PARIS Tel. (1) 40 62 43 03
Principal investigator	Elisabeth AUBENY, M.D. Centre d'Orthogénie Hôpital BROUSSAIS 96, rue Didot 75014 PARIS Tel. (1) 43 95 95 95

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APPEARS THIS WAY
ON ORIGINAL

1. INTRODUCTION

Mifepristone (RU 486, Mifegyne®) is an antiprogesterone compound synthesised by ROUSSEL UCLAF. Previous studies have shown that it is capable by itself to terminate about 80% of pregnancies of less than or equal to 41 days of amenorrhoea (DA) (1) when given in a single dose of 600 mg orally. After this date the efficacy of the compound alone decreases rapidly (a reduction of about 10% in the success rate for each additional week of amenorrhoea). Swedish (2), Scottish (3) and French (4-5) studies have shown that the combination of mifepristone with a synthetic prostaglandin analogue (sulprostone or gemeprost) achieves the complete termination of pregnancy in 95% of cases of amenorrhoea of up to 49 days. These studies also indicate that the combination of mifepristone + prostaglandin reduces the doses of prostaglandin necessary (0.25 mg for sulprostone, 0.5 or 1.0 mg for gemeprost), and hence their side-effects.

The optimum interval between administration of mifepristone and administration of the prostaglandin is 36 to 48 hours. In fact, the cervical dilatation induced by mifepristone is greater at 48 than at 24 hours and maximum sensitisation of the uterine muscle to the contracting action of prostaglandins occurs 36 to 48 hours after administration of mifepristone (6, 7).

Mifepristone has been registered in France as a medical alternative to uterine aspiration for pregnancies of less than 50 DA. It is prescribed in a single dose of 600 mg (3 tablets of 200 mg) in a single dose and is followed 36 to 48 hours later by administration of 1 mg of gemeprost or 0.25 mg of sulprostone

In a study in about 16,000 women (8), the tolerance of this method of pregnancy termination was good. In the 4 hours following prostaglandin administration painful uterine contractions occurred in about 80% of women. These contractions required treatment in 20 to 60% of patients depending on the dose of prostaglandin used (1 mg of gemeprost, 0.25 or 5 mg of sulprostone). During this period nausea (34% of women), vomiting (15% of cases) and diarrhoea (7.5% of cases) were observed. Malaise (lipothymia or hypotension), was also reported in about 1% of cases.

The uterine bleeding required a haemostatic endo-uterine procedure in 0.8% of cases and a transfusion in 0.1% of cases.

In all the women having recoursed to this method (about 60,000) 3 severe cardiac adverse events (myocardial infarction) have been reported, with a fatal outcome in one of the cases. These infarcts appear related to a coronary spasm and all occurred within 4 hours following the injection of sulprostone. The 3 patients concerned were all over the age of 30 years and smokers. These coronary spasms are very probably attributable to sulprostone and have also been described after isolated injection of sulprostone (9).

In view of these accidents, it was decided to investigate if other prostaglandins than those studied previously could be associated with mifepristone.

Misoprostol is a synthetic derivative of the PGE_1 series (15-desoxy-16-hydroxy-16-methyl analogue) administered orally at a dose of 4 tablets of 0.2 mg daily for gastric or duodenal ulcers (10).

The compound is very widely prescribed. At a dose of 4 tablets of 200 µg daily it does not cause hypotension and its cardiovascular tolerance appears to be good. No serious cardiovascular effect has been published to date and the pharmacovigilance data are favourable (11).

This prostaglandin can stimulate the contraction of smooth muscle fibre, particularly of the uterus.

A preliminary study in 100 women (12) showed that administration of 600 mg of mifepristone followed 48 hours later by 2 tablets of misoprostol achieved the termination and complete expulsion of 95% of pregnancies of not more than 49 days of amenorrhoea. The tolerance of the method was satisfactory. The main adverse effects were nausea (35 cases), vomiting (11 cases) and diarrhoea (7 cases), symptoms which did not require treatment. By contrast, however, the intensity of the uterine pain appeared to have been very markedly decreased in comparison with the prostaglandins used previously (sulprostone, gemeprost). The duration of bleeding was not affected.

It therefore appears of interest, in view of all the previous information, to confirm the efficacy and tolerance of this combination in a large-scale study.

2. STUDY OBJECTIVE

The aim of this study is to evaluate the efficacy and tolerance of the use of mifepristone (600 mg) in combination with 2 tablets of 0.2 mg of misoprostol administered 48 hours later in the termination of pregnancies of less than or equal to 49 days of amenorrhoea and under the law on abortion in France.

3. STUDY DESCRIPTION

It is a multicentre, open study assessing the following therapeutic regimen:

- Mifepristone will be administered at a dose of 600 mg (3 tablets of 200 mg) in the presence of the investigator on Day 1 after verification of the inclusion criteria.

- Misoprostol (2 tablets of 0.2 mg in a single dose) will be administered 48 hours later on the morning of Day 3, also in the presence of the investigator. The woman will be kept under observation at the hospital for 4 hours.

The efficacy and tolerance of the treatment will be assessed at a follow-up visit 8 to 15 days after administration of mifepristone.

4. SUBJECT SELECTION

4.1 Number

The scheduled number of patients is 500. These patients will be recruited in 24 centres.

4.2 Inclusion criteria

The following women will be included:

a) requesting a pregnancy termination,

b) having satisfied the compulsory legal requirements for abortion in France,

c) between the ages of 18 (legal majority; women below the age of majority may only be included with the consent of their legal guardian) and 35 years,

d) having agreed to comply with the restrictions of the study, particularly the follow-up visit after administration of the treatment,

e) informed of the normal procedure for an abortion,

f) agreeing to undergo an instrumental termination of pregnancy in the event of treatment failure,

g) informed of the study procedure and having given their written consent to participate in it (Appendix 1),

and whose pregnancy is:

- intra-uterine,

- on-going,

- of specified age and less than or equal to 49 days of amenorrhoea (calculated from the first day of the last menstrual period).

(A pregnancy with an IUD in situ is not a contra-indication if it is removed when mifepristone is taken).

4.3 Exclusion criteria

The following women will not be included:

a) with signs of a miscarriage,

b) with a suspected ectopic pregnancy,

c) with amenorrhoea of more than 49 days,

d) over the age of 35,

e) smokers, defined as smoking at least 10 cigarettes daily during the two years preceding the beginning of the study,

f) having one of the following disorders: a history of cardiovascular disease (angina pectoris, rhythm disorders, heart failure, severe hypertension, etc.), asthma, glaucoma or raised intra-ocular pressure, diabetes, hyperlipidaemia.

g) with a current or previous history of renal, adrenal or hepatic insufficiency,

h) having received chronic corticosteroid therapy within the previous 6 months,

i) having a known abnormality of haemostasis or receiving anticoagulant treatment,

j) having a known allergy to mifepristone,

k) with anaemia,

l) refusing to give their written consent to participate,

m) considered liable not to comply with the requirements of the protocol or who live too far away from the centre.

5. STUDY DRUGS

5.1 Mifepristone

Mifepristone will be supplied by Laboratoires Roussel in the form of tablets containing 200 mg of micronised active substance. The tablets will be packaged in blister packs containing 3 tablets.

The compound will be given in a single dose of 3 tablets in the presence of the investigator from a distance of a meal.

The boxes of mifepristone will be labelled:

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

All the boxes of mifepristone necessary for one centre will be given to the responsible pharmacist within this centre who will distribute them to the investigator.

After the inclusion and exclusion criteria have been checked, the woman will be allocated a study entry number and given a box marked with this number. The numbers will be allocated in order.

A trial drug accountability form must be kept by the investigator.

At the end of the study all unused compounds and the drug accountability form must be recovered by the clinical research assistant.

5.2 Prostaglandin analogue

The prostaglandin analogue used will be misoprostol (Cytotec®). It will be administered 48 hours after administration of mifepristone in a single dose of 2 tablets of 0.2 mg in the presence of the investigator. The woman will then be kept under monitoring at the centre for 4 hours.

Misoprostol will be supplied to the responsible pharmacist of the centre by Laboratoires Roussel.

5.3 Concomitant medications

5.3.1 Permitted medications

As far as possible no other medications will be given concomitantly. Where a drug is prescribed, the type and dose of the medication will be entered in the case report form.

Current treatments will be reported in the case report form.

5.3.2 Prohibited medications

Acetylsalicylic acid and its derivatives, steroidal and non-steroidal anti-inflammatories, prostaglandin synthesis inhibitors (where necessary an analgesic belonging to another pharmacological class or an antispasmodic will be used in preference to one of these medications), enzyme-inducing medications.

Oxytocics or prostaglandins other than that used in the study.

The patient must refrain from self-medication.

The patient must refrain from smoking and drinking alcohol during the 48 hours between administration of mifepristone and misoprostol and on the day of administration of misoprostol.

6. ASSESSMENT CRITERIA

6.1 Efficacy

The efficacy will be assessed between 8 and 15 days after administration of mifepristone (Day 8 - Day 15) by the investigator on the basis of the clinical data (occurrence of bleeding, expulsion of the ovum, persistence of bleeding), laboratory data and/or ultrasound data.

A distinction will be made between the following:

1) The termination and complete expulsion of the pregnancy (disappearance of clinical signs, fall in beta HCG compared with Day 1 and/or an empty uterus on ultrasound) without the need for a supplementary surgical procedure (apart from the forceps extraction of ovular fragments protruding through the external os, where necessary). The date and if possible the time of expulsion will be noted. This possibility will be considered a success.

2) Pregnancy termination without complete expulsion.

3) On-going pregnancy.

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

Eventualities 2, 3 and 4 will be followed by a supplementary surgical procedure, the date of which will be noted. These cases will be considered failures.

6.2 Tolerance

6.2.1. At the time of administration of misoprostol (Day 3):

Tolerance will be evaluated on the basis of the following information:

Any adverse event occurring between Day 1 (administration of mifepristone) and Day 3.

The onset within 4 hours after administration of misoprostol of painful uterine contractions and gastro-intestinal disorders: nausea, vomiting, diarrhoea. The intensity of these symptoms will be noted and whether or not symptomatic treatment is required.

Hourly observation during the 4 hours following administration of misoprostol of blood pressure (systolic and diastolic) and heart rate.

The occurrence of an adverse effect other than those mentioned above.

6.2.2. At the follow-up visit (Day 8 - Day 15):

Tolerance will be evaluated on the basis of the following:

The duration of uterine bleeding and the need for specific measures: measurement of haemoglobin concentration, drug treatment, blood transfusion, haemostatic surgical procedure.

Any unusual clinical signs or symptoms occurring since Day 3.

6.2.3. Laboratory safety

This will be assessed on the haemoglobin level measured on Day 1 (before administration of mifepristone) and on Day 8 - Day 15 during the follow-up visit.

7. STUDY PROCEDURE

7.1 Initial assessment (Day 1)

Check that the patient has undertaken the necessary legal steps for a request for abortion and has fulfilled the conditions laid down by the law (reflection period).

a) Note:

- any previous history,
- any treatment in progress and its reason,
- the date of the last menstrual period.

b) Check that the gestational age is less than or equal to 49 days of amenorrhoea.

c) Perform an assay of βHCG or a uterine ultrasound.

d) Determine the Rhesus group if the patient does not have a blood group card and measure the haemoglobin level.

e) Give the patient an information sheet about the study and obtain her written consent to participate.

f) Allocate the woman a study enrolment number and give her the 3 tablets of mifepristone contained in the box bearing this number. Treatment will be taken immediately in the presence of the investigator. The number will be noted on the case report form.

g) Inform the woman that she must refrain from smoking and drinking alcohol during the following 48 hours and on Day 3.

h) Make an appointment for two days later in the morning (Day 3).

7.2 Day 3: Administration of misoprostol:

- Clinical examination

- Investigation of any adverse event.

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

- Administration of 2 tablets of 0.2 mg of misoprostol in a single dose (if expulsion has not already occurred) in the presence of the investigator.

- The patient must remain under observation in the centre during the following 4 hours.

- During these 4 hours of observation the following parameters will be assessed:

  - Painful uterine contractions, nausea, vomiting and diarrhoea, by means of the following scale:

    1: minimal
    2: moderate
    3: severe, not requiring treatment
    4: severe, requiring treatment

  * The overall intensity of the pain during this observation will also be evaluated on a visual analogue scale 4 hours after administration of misoprostol.

  * If premedication has been given, this will be noted in the case report form.

  * The drugs administered will be noted in the case report form.

- Heart rate, systolic and diastolic blood pressure measured hourly.

- The moment of ovular expulsion will be noted if it occurs during the time when the patient is under observation.

- If the patient experiments chest pain, a rhythm disorder or hypotension, an ECG must be performed. In the event of severe pain, fast-acting nitrate derivatives will be prescribed under the assumption of a coronary spasm.

- At the end of 4 hours the woman is allowed to leave the centre and given an appointment for Day 8 - Day 15 with a prescription for an assay of haemoglobin immediately before this visit.

- Oral contraception, to be started 24 to 48 hours later, can be prescribed at this visit.

7.3 Day 8 - Day 15: Follow-up visit:

- Further clinical examination and assessment of tolerance by the investigator.

- If possible, note the date of ovular expulsion and the interval between expulsion and prostaglandin administration.

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

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

- Evaluation of uterine bleeding:

a) duration,
b) was an emergency measurement of the haemoglobin concentration necessary (note the result)?

- Has treatment been necessary (drug, transfusion, haemostatic surgical procedure)?

- In the event of failure (on-going pregnancy, incomplete expulsion), recommend a supplementary surgical procedure.

- Note the results of the assay of haemoglobin.

8. COLLECTION AND ANALYSIS OF DATA

8.1. Collection of data:

A case report form will be completed for each patient admitted in the study. Only the investigator and his colleagues are qualified to complete the case report form and make any corrections on it.

Corrections of data on the case report form can be made only by crossing through the incorrect entry so that it remains visible and putting the correct figure by the side. The correction must be initialled and dated in the margin by the person making the correction. Each case report form must be signed and dated by the investigator.

8.2. Analysis of data:

The analysis of the data will be performed by the Biometry Department of Laboratoires Roussel. It will be primarily descriptive.

9. PROTOCOL AMENDMENTS

No changes may be made to a protocol without the written agreement of Roussel.

Any modification must be the subject of a documented amendment justified in writing. It must be signed by the investigator indicating his acceptance of the change to the study procedure.

This protocol amendment must be submitted to and approved by the Ethics Committee if it is likely to affect adversely the expected medical benefit/risk ratio for the patient.

If the protocol modification is necessary immediately in order to ensure the safety of the patients, those responsible for the study will submit the amendment to the Ethics Committee after its application as rapidly as possible.

10. SIDE-EFFECTS AND ADVERSE EVENTS

10.1. Serious adverse event:

A serious adverse event is defined as:

- Any event with a fatal outcome or which is life-threatening.
- Any event leaving sequelae or following a chronic course.
- Any event necessitating hospitalisation or the prolongation of hospitalisation.
- The discovery of a congenital abnormality or cancer.
- An overdosage.

All serious adverse events must be notified immediately to Laboratoires Roussel:

- **Rémi PEYRON, M.D.** Tel. 1 40 62 41 40 Fax. 1 40 62 49 68

OR

- **Louise SILVESTRE, M.D.** Tel. 1 49 91 46 60 Fax. 1 49 91 49 49 or 1 49 91 48 00

OR

Tel. 1 40 62 48 65
Fax. 1 40 62 49 68

Written confirmation must be sent in the form of the adverse event record form (a copy of which is included in Appendix 2) either by fax or by urgent mail.

10.2. Mild adverse events:

These will simply be reported in the case report form.

11. WITHDRAWALS AND DEFAULTERS

Any patient enrolled in the study will be analysed for tolerance. Only women completing the study may be analysed for efficacy.

12. NOTIFICATION TO REGULATORY AUTHORITIES

The study will be declared to the Ministry of Health.

13. ETHICS

This study will be conducted in accordance with the principles of the Declaration of Helsinki (cf. Appendix 3) and French law on clinical trials.

13.1. Consent:

Prior to the patient's inclusion in the study her written consent will be obtained (signed by the patient and the signature preceded by "read and approved"). In order to obtain this consent, she will be given an information document on the study (Appendix 1).

In addition the investigator will sign an identification and consent obtained form "thereby attesting to the fact that the patient's consent has been obtained".

13.2. Ethics Committee:

The protocol will be submitted to an Ethics Committee.

The study may only begin after Laboratoires Roussel has received a copy of the written approval from this Committee.

In the event of a protocol amendment, this amendment must be submitted to and approved by the Ethics Committee if it is liable to affect adversely the medical benefit/risk ratio for the patients.

14. CONFIDENTIALITY

The data obtained during the study are considered to be confidential.

The information supplied by Laboratoires Roussel (product brochure, protocol, case report form) are also confidential.

For each patient the data will be identified by the patient's number in the study and by her initials and will be processed anonymously in the analyses.

All the data relating to the study must be accessible to other investigators participating in it, the Laboratoires Roussel Co-ordinator, the Head of Quality Assurance, the Ethics Committee and the Regulatory Authorities.

15. STUDY MONITORING AND QUALITY CONTROL

Members of Laboratoires Roussel will make regular contact with the investigator by means of on-site visits and telephone calls to monitor the procedure of the study and to ensure that it is conducted in compliance with the protocol.

The case report forms will be reviewed in detail at each visit.

The investigator and his team undertake to co-operate with the monitor and in particular to provide him with the documents and missing information whenever possible.

Each case report form will be signed by the investigator who must initial and date any corrections.

If there are any missing or unavailable data the reason for this must be stated.

Participation in the study implies that the investigator agrees to the possibility of a quality assurance audit to check that the procedures described in the protocol have been followed throughout the study.

16. STUDY DURATION

The study will begin in June 1991 and will last about 3 months.

17. INSURANCE

The investigator's civil liability in the context of this study is covered by an insurance policy taken out by Laboratoires Roussel (Appendix 4).

18. PUBLICATION

Any communication or publication of the results of this study will be the subject of a previous agreement between the investigators and Laboratoires Roussel.

19. DECLARATION AND RESPONSIBILITY OF INVESTIGATOR

All the information relating to the trial drug and the results of the study are considered to be confidential.

I have read the protocol and I consider that it contains all the information necessary for the conduct of the study.

I undertake to carry out this study in compliance with this protocol and will not modify it in any way without the written approval of Laboratoires Roussel.

I undertake not to begin the study before an Ethics Committee has given its approval.

I will conduct the study in accordance with the principles laid down in the Declaration of Helsinki and in compliance with Good Clinical Practice. In particular I will obtain the written informed consent of each patient before her admission to the study.

Furthermore, I also undertake to complete the case report forms carefully, to comply with the procedure in the event of a serious side-effect and to be responsible for the handling of the trial drug.

I agree to the monitoring of the study by a member of Laboratoires Roussel and to the possibility of a quality assurance audit.

I will make all data and information directly concerning the study available to Laboratoires Roussel and the Regulatory Authorities.

I will retain the raw data obtained during this study for a period of 10 years.

Drug name: MIFEPRISTONE
Protocol No.: FFR/91/486/14

Date

Signature of investigator

Date

Signature of the Laboratoires Roussel Co-ordinators

APPEARS THIS WAY

REFERENCES

1. Brochure given to the investigator

2. **M. BYGDEMAN, M.L. SWAHN** - Progesterone receptor blockade. Effect on uterine contractility and early pregnancy. Contraception, 1985, 32, p. 45-51.

3. **M.W. RODGER, D.T. BAIRD** - Induction of therapeutic abortion in early pregnancy with mifepristone in combination with prostaglandin pessary. Lancet, 1987, 2, p. 1415-1418.

4. **C. DUBOIS, L. SILVESTRE, A. ULMANN** - Utilisation de la Mifépristone dans l'interruption volontaire de grossesse. Expérience Française. Presse Méd., 1989, 18, p. 757-760.

5. **L. SILVESTRE, C. DUBOIS, M. RENAULT, Y. REZVANI, E.E. BAULIEU, A. ULMANN** - Voluntary interruption of pregnancy with mifepristone (RU 486) and a prostaglandin analogue. A large-scale French experience. N. Engl. J. Med., 1990, 322, p. 645-648.

6. **Y. LEFEBVRE, L. PROULX, R. ELIE, O. POULIN, E. LANZA** - The effects of RU 38486 on cervical ripening. Clinical Studies. Am. J. Obstet. Gynecol., 1990, 162, p. 61-65.

7. **M.L. SWAHN, M. BYGDEMAN** - The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. Br. J. Obstet. Gynaecol., 1988, 95, p. 126-134.

8. ———————————————————

9. **E. ELIERS, D. DUREN, P.A. VAN ZWIETEN** - A prostaglandin analogue as a probable cause of myocardial infarction in a young woman. Brit. Med. J. 1991, 302, 416.

10. **R.L. HERTING, C.H. NISSEN** - Overview of misoprostol clinical experience. Dig. Dis. Sci., 1986, 31 (supplement), p. 47S-54S.

11. **R.A. WILDEMAN** - Focus on misoprostol: Review of worldwide safety data. Clin. Invest. Med. 1987, 10, 243-245.

12. **E. AUBENY, E.E. BAULIEU** - Activité contragestive de l'association au RU 486 d'une prostaglandine active par voie orale. C.R. Acad. Sci., Paris (in press).

CHECK - LIST

DAY 1: INCLUSION:

- Confirmed pregnancy following a normal course.

- Unambiguous request for an abortion, legal procedures observed.

- Amenorrhoea of less than or equal to 49 days.

- Age more than 18 years (or consent of the legal guardian in the case of patients under the age of majority), and less than or equal to 35 years.

- No contra-indication to the method.

- Explain to the patient the procedure for an abortion and the details of the protocol, obtain her written consent.

- Assay of βHCG and/or ultrasound.

- Assay of haemoglobin, blood group.

- Have the patient take 600 mg (3 tablets of 200 mg) of mifepristone in a single dose in the presence of the investigator.

- Notify the patient of the requirement to refrain from smoking and drinking alcohol during the following 48 hours and on Day 3.

- Appointment for Day 3.

DAY 3: ADMINISTRATION OF MISOPROSTOL:

- Injection of anti-D gamma-globulins if the patient is Rhesus negative.

- Record any symptoms occurring after administration of mifepristone.

- Check that expulsion has not occurred between Day 1 and Day 3.

- In the absence of expulsion, administration of misoprostol: 2 tablets of 0.2 mg in a single dose.

- Monitoring during the 4 hours following this administration:

  . Measure heart rate, systolic and diastolic blood pressure hourly.

  . Investigation of painful uterine contractions, nausea, vomiting, diarrhoea; evaluate their intensity and note any treatment given.

- Appointment for Day 8 - Day 15 with a prescription for an assay of haemoglobin.

- Possible prescription of oral contraception to be instituted 24 to 48 hours later.

DAY 8 - DAY 15: FOLLOW-UP VISIT:

- Evaluation of the efficacy and tolerance of treatment.

- If possible, note the date and time of ovular expulsion.

- Note the results of the assay of haemoglobin.

- In the event of failure (on-going pregnancy or uterine retention), recommend a supplementary surgical procedure.

APPENDIX 1

- Patient information form

- Written consent record form.

APPEARS THIS WAY
ON ORIGINAL

READ THIS NOTICE CAREFULLY AND ASK YOUR DOCTOR TO EXPLAIN ANY POINTS WHICH ARE NOT CLEAR TO YOU.

BEFORE TAKING MIFEGYNE, THE DOCTOR WILL ASK YOU TO SIGN A FORM STATING THAT YOU HAVE READ AND UNDERSTOOD THIS NOTICE.

PATIENT INFORMATION

You have requested a termination of your pregnancy. It is proposed that you should participate in a study intended to evaluate on a large scale the efficacy of the combination of Mifegyne and an oral prostaglandin, misoprostol, in the termination of pregnancy.

This study complies with the law on clinical trials and the principles of the Declaration of Helsinki. It has been submitted to the Ethics Committee of the following Hospital
which granted its approval on

A preliminary study has been performed in 100 women and shows that this method appears as effective as that used currently, which combines Mifegyne with a prostaglandin . It is necessary to confirm these results on a larger scale and 500 women will participate in this study. They will be recruited in 24 public or private hospital centres.

Mifegyne is a drug which blocks the action of progesterone, a pregnancy maintenance hormone. Its action however requires to be completed 36 to 48 hours later by that of a prostaglandin, a substance which increases uterine contractions.

Mifegyne may only be used in accordance with the regulations in force on abortion (laws of 1975 and 1979).

The three tablets of Mifegyne must be taken within 49 days after the first day of your last menstrual period.

Mifegyne may not be used in the following cases:

- if the pregnancy is not confirmed,
- in the event of a suspected ectopic pregnancy,
- if the first day of your last menstrual period is more than 50 days
- if you are over the age of 35,
- in the event of one of the following diseases: renal failure, hepatic failure, adrenal insufficiency, abnormality of blood coagulation or administration of an anticoagulant medication, anaemia, asthma or a history of asthma, a history of cardiovascular disorders (angina pectoris, rhythm disorder, heart failure, severe hypertension), diabetes, hyperlipidaemia, glaucoma or raised intra-ocular pressure.
- in the event of prolonged treatment with corticosteroids,
- if you are a smoker (at least 10 cigarettes daily in the previous 2 years).

TERMINATION OF PREGNANCY WITH MIFEGYNE INVOLVES CONSTRAINTS AND IMPLIES RESTRICTIONS OF WHICH YOU MUST BE AWARE

1. It is mandatory that administration of Mifegyne is followed 36 to 48 hours later by the administration of a prostaglandin to obtain the maximum efficacy of the method.

2. Mifegyne is not 100 per cent effective and you cannot by yourself assess the efficacy of the method.
In fact, the uterine bleeding which occurs is not a proof of efficacy and the expulsion of the ovum which often occurs a few hours after administration of the prostaglandin may be incomplete.

It is compulsory for you to attend a follow-up visit 12 to 15 days after administration of Mifegyne to check that your pregnancy has indeed been terminated.

In the event of a failure, the termination of pregnancy or the evacuation of placental debris can only be obtained by surgical methods.

3. As with any termination of pregnancy uterine bleeding (metrorrhagia) will occur in almost all cases. This is sometimes very heavy and may in that case involve an emergency treatment. You should not move too far away from the prescribing centre until the follow-up visit and the doctor will indicate to you where you should telephone or go in the event of an emergency.

4. Abdominal pain requiring treatment, nausea, vomiting, diarrhoea or malaise can occur in some cases after administration of the prostaglandin, which therefore entails observation for a few hours in the prescribing centre.

5. THE FOLLOW-UP VISIT ALLOWS TO CHECK WHETHER THE PREGNANCY HAS BEEN TERMINATED. IN FACT IF THE PREGNANCY WERE TO CONTINUE AFTER ADMINISTRATION OF MIFEGYNE AND THE PROSTAGLANDIN THE FOETUS OR THE FUTURE CHILD ARE LIABLE TO BE MALFORMED.

6. The occurrence of a further pregnancy is possible immediately after the termination of the pregnancy: if you do not wish to have a further pregnancy, contraception must be instituted early on.

7. If you belong to a Rhesus negative blood group, Rhesus immunisation must be prevented.

8. Exceptional cases of cardiovascular accidents have been reported after the injection of a prostaglandin. Consequently the Mifegyne-prostaglandin analogue method is contre-indicated where there is an increased cardiovascular risk from the following factors: smoking, hyperlipidaemia, diabetes, hypertension, cardiovascular history age over 35 years.

9. You must refrain from SMOKING and drinking alcohol during the two days between administration of Mifegyne and administration of the prostaglandin, and on the day of administration of the prostaglandin.

In addition, the study may be discontinued:

a) from medical reasons of which the doctor will be the judge,

b) or at your own request, without any justification being required of you.

A uterine evacuation will then be undertaken at your request and under medical supervision.

In the event of an emergency, or for any other question relating to this study, you can contact by telephone:

on number:

. Dr.

APPEARS THIS WAY
ON ORIGINAL

PRACTICAL PROCEDURE OF THE METHOD

DAY OF THE FIRST CONSULTATION

- You are requesting an abortion

- The first day of the last menstrual period is no more than 42 days previously.

- From this Day 0 you have one week for reflection (in accordance with the law on abortion).

ONE WEEK LATER - 2nd STAGE:

- You confirm your request for an abortion.

- You have no contra-indication to the use of Mifegyne and prostaglandin.

- You have read the information notice on Mifegyne, you have obtained any additional information which you require, and you have signed the form confirming that you have been informed.

- You swallow 3 tablets of Mifegyne in the presence of the doctor (Day 1)

- You will return home with a further appointment 48 hours later, knowing where to telephone or to go in the event of an emergency.

- The uterine bleeding usually begins one or two days later.

TWO DAYS LATER (DAY 3):

- You return to the prescribing centre.

- The prostaglandin is administered (2 tablets in a single dose)

- You remain resting for a few hours in the centre and then you return home with, if necessary, a prescription for an oral contraceptive.

- Expulsion of the ovum occurs while you are in the centre or within the following few days.

- The bleeding persists usually until the follow-up visit.

FOLLOW-UP VISIT: 5 to 13 days after administration of the prostaglandin.

You return to the prescribing centre for the follow-up visit: the doctor will check that expulsion is complete. In the event of an on-going pregnancy or incomplete expulsion the prescriber will recommend a surgical technique (aspiration).

WRITTEN INFORMED CONSENT

Protocol No.:

Study title:

I, the undersigned: _____ APPEARS THIS WAY ON ORIGINAL

living at: _____

_____

_____

agree, in full awareness of the facts and of my own volition, to participate in the medical research

conducted by Doctor _____

The medical information obtained during the study is confidential. My identity will not be disclosed in the reports or publications to which this study may give rise.

I am aware that I may refuse to participate in this research or that I may withdraw my consent at any time without incurring any liability on my behalf.

I certify that the objective of the research, the conditions of its performance and its duration have been clearly indicated to me, together with the restrictions and foreseeable risks, including in the event of the research being terminated before its completion. A summary of this information has been given to me.

Treatment number allocated

|_|_|_|

Place: _____

Date _____

APPEARS THIS WAY ON ORIGINAL

Signature of the subject, preceded by "Read and approved"

- The original is to be kept by the investigator for a minimum of 10 years

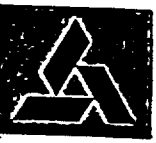
APPENDIX 2

- Serious adverse event record form.

APPEARS THIS WAY
ON ORIGINAL

DRUG SURVEILLANCE DEPARTMENT - ROUSSEL UCLAF

CLINICAL TRIAL
SERIOUS ADVERSE EVENT FORM



➤ TO BE COMPLETED IN CASE OF :

- Life-threatening event
- Death
- Cancer/congenital anomaly
- Event leading to hospitalisation or prolongation of hospitalisation
- Event resulting in chronic condition/sequelae
- Overdose

APPEARS THIS WAY ON ORIGINAL

WHATEVER RELATIONSHIP TO STUDY DRUG

➤ The first copy must be sent to the monitor, the second must be kept by the investigator, the third must be enclosed in the case record form.

➤ Please be as complete and as precise as possible when describing the course of the patient's condition.
If possible, please join a copy of the relevant investigations and forward a hospitalisation report when available.

CLINICAL TRIAL
SERIOUS ADVERSE EVENT FORM

BEST POSSIBLE COPY

STUDY/INVESTIGATOR

Protocol number : ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Center number : ⌊_⌊_⌊_⌊_⌋

Indication : _____

_____

Investigator's name : _____

Address : _____ Country : _____

_____

_____

PATIENT

Number allocated in the study ⌊_⌊_⌊_⌊_⌊_⌋

Local drug surveillance number ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Initials	Age	Sex	Weight	Height
⌊_⌊_⌊_⌋	⌊_⌊ y ⌊_⌊ m	M ⌊_⌋ F ⌊_⌋	⌊_⌊_⌋ kg ⌊_⌊_⌋ g	⌊_⌊ m ⌊_⌊ cm

Occupation : _____ Ethnic origin : _____

Previous relevant history : _____

_____

_____

_____

Previous Intolerance to drugs : No ⌊_⌋ Yes ⌊_⌋ which drugs ? _____

_____

Unknown ⌊_⌋

ADVERSE EVENT

Date of onset ⌊_⌊ D ⌊_⌊ M ⌊_⌊ Y

Description : _____

_____

Hospitalisation (or prolongation of hospitalisation) necessary ? ⌊_⌋ yes ⌊_⌋ no

Treatment : _____

_____

_____

OUTCOME : Complete recovery ⌊_⌋ Chronic condition or sequelae ⌊_⌋

Not yet resolved ⌊_⌋ Unknown ⌊_⌋

Death ⌊_⌋

➤ Date ⌊_⌊ D ⌊_⌊ M ⌊_⌊ Y

➤ Autopsy ⌊_⌋ yes ⌊_⌋ no

➤ Cause of death _____

CASE SUMMARY

(Precise description of history with respect to the adverse event)

APPEARS THIS WAY
ON ORIGINAL

STUDY DRUG

Name _____

or Code ⌊⌊⌊⌊⌊⌊⌊⌊

Daily dose regimen : dose ⌊⌊ unit ⌊⌊ frequency ⌊⌊

Route _____

Therapy date : from ⌊⌊ ⌊⌊ ⌊⌊ (D M Y) to ⌊⌊ ⌊⌊ ⌊⌊ (D M Y) Ongoing ⌊

Action taken with study drug after the event :

Continued same dose ⌊ Stopped ⌊ Decreased ⌊ NA* ⌊

Immediate results :

Improvement ⌊ No change ⌊ Aggravation ⌊ Uninterpretable ⌊ NA* ⌊

Rechallenge

No ⌊ Yes ⌊ NA* ⌊

Date : ⌊⌊ ⌊⌊ ⌊⌊ (D M Y)

Recurrence of event :

No ⌊ Yes ⌊ Uninterpretable ⌊ NA* ⌊

* Not applicable

CONCOMITANT DRUGS

Drug	Daily dose	From	To	Indication

CAUSAL RELATIONSHIP

Doctor's assesement :

Unrelated ⌊ Unlikely ⌊ possible ⌊ probable ⌊ highly probable ⌊

not assessable ⌊ explain why _____

This form was filled out ➤ on ⌊⌊ ⌊⌊ ⌊⌊ (D M Y)

➤ by (print)

➤ position

➤ signature : 110 d

➤ Monitor's name and signature : _____ 1379

APPENDIX 3

Declaration of Helsinki

WORLD MEDICAL ASSOCIATION
DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may effect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports on experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of a patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NONTHERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue to research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX 4

Insurance

9. RESULTS - SAFETY

Adverse events

Metrorrhagia

Frequency (Table 24)

Of the 1103 patients seen at the follow-up visit and for whom the information was available, 1099 (99.6%) had uterine bleeding. Four patients had no bleeding (No. 32: retention requiring a surgical procedure. No. 769, 799, 1072: ongoing pregnancies).

Interval between administration of mifepristone and the onset of metrorrhagia (Table 21)

Among the 1097 cases for which the information is known, the mean interval was 1.69 days ± 0.98 (s.d.) (range -1 to 19 days) and the median 2 days

Interval between the first administration of misoprostol and the onset of metrorrhagia (Table 22)

Among the 1070 patients having received misoprostol and for whom the information is available, the mean interval was -0.29 ± 0.98 days (s.d.) (range -2 to + 17 days) and the median 0 days. In 31.8% of the women (341 out of 1070), bleeding started before the administration of misoprostol.

Duration of bleeding (Tables 23.1, 23.2, 23.3)

In the 1031 patients for whom the information is available and in whom bleeding had ended at the control visit, the mean duration of bleeding was 9.33 days ± 4.74 (s.d.) (range 1 to 69 days). The median was 8 days.
In 845 patients out of 1066 (79.2%) the bleeding lasted 12 days or less.
The individual data relating to metrorrhagia are given in Appendix 8.

Action taken for bleeding (Tables 10.1, 24, Appendix 6)

Ten patients (0.9%) had to undergo a haemostatic surgical procedure. This involved the following cases, all of which (except No. 633) were considered serious adverse events (cf. paragraph):

- patient No. 633 underwent an aspiration of clots retained in the cervix on D_3 at the end of the monitoring period

- patient No. 1178 was hospitalised for metrorrhagia two days after administration of mifepristone. She took two tablets of misoprostol at the centre. The bleeding became heavier and was accompanied by collapse. The patient then had a haemostatic curettage under general anaesthesia.

- patients No. 122 and No. 348 had a haemostatic curettage during the monitoring period in the centre (curettage under general anaesthesia for patient No. 348)

- patients N° 980 and N° 1076 had a haemostatic curettage on D_3 after the monitoring period scheduled in the protocol

- patients No. 63, No. 333, No. 532 and No. 668 had a dilatation and curettage between D_4 and D_7.

The percentage of haemostatic surgical procedures increased with gestational age: 0% for pregnancies of less than 42 days of amenorrhoea, 0.3% (n = 1) between 42 and 49 days of amenorrhoea, 0.8% (n = 3) between 50 and 56 days of amenorrhoea and 2.6% (n = 6) between 57 and 63 days of amenorrhoea (Table 10.1).

Fisher's exact test comparing the number of haemostatic procedures for pregnancies of ≤49 days versus pregnancies > 49 days showed a significant difference (p = 0.049).

Three patients (Nos. 751, 880 and 1117) had a blood transfusion (anaemia discovered during the follow-up visit (No. 751 and 880), ruptured and operated ectopic pregnancy (No. 1117: excluded from the analysis of efficacy)).

Variations in haemoglobin level (Table 25) (Appendix 9)

Of the 1028 patients for whom the information is known, the mean variation in the haemoglobin level at the follow-up visit (D_{10} - D_{18}) from D_1 (administration of mifepristone) was -0.8 g/dl ± 1.1 (s.d.) (range: -6.4 to +3.1).

Two hundred and two women (19.7%) had no fall in haemoglobin levels. 481 women (46.8%) lost between 0 and 1 g/dl of haemoglobin, 219 (21.3%) between 1 and 2 g/dl and 126 (12.2%) more than 2 g/dl. Four patients had a loss of between 5 and 7 g/dl of haemoglobin (No. 333, No. 880, No. 1178 and No. 1184). Among these women only patient No. 880 received a blood transfusion. Regarding the other two patients who were transfused: patient No. 751 had a variation in haemoglobin levels of -3.7 g/dl; patient No. 1117 underwent surgery for a ruptured ectopic pregnancy but the postoperative haemoglobin level is not known.

Gastro-intestinal signs observed between administration of mifepristone and administration of misoprostol (Table 26) (Appendix 10)

Nausea

Three hundred and fifty patients out of 1194 for whom the information is known (29.31%) had nausea during this interval.
The intensity of these nausea was mild in 35.41% of cases, moderate in 39.09% and severe in 25.5%.

Vomiting

One hundred and seventy-two patients out of 1194 (14.41%) had vomiting, which was of mild intensity in 49.13% of cases.

Of the 522 women who suffered from nausea and/or vomiting, 30 required treatment.

Diarrhoea

Thirty-nine patients out of 1194 (3.27%) had an episode of diarrhoea.
This was of mild intensity in 52.5% of cases.
Treatment was necessary in 5.13% (2/39) of cases.

Clinical signs observed within 3 hours after the first administration of misoprostol

Pelvic pain (Table 27) (Appendix 11) (Figure No. 2)

During the 3 hours of monitoring following the first administration of misoprostol, painful uterine contractions were reported in 937 out of 1164 patients (80.5%) having received misoprostol (Table 27).

In 192 of these 1164 patients (16.49%) analgesic treatment was prescribed. The most widely prescribed medication was phloroglucinol (Table 37).

The intensity of pain was evaluated in 1156 patients at the end of the monitoring period on D_3 by means of a visual analogic scale ranging from 0 (no pain) to 100 mm (intolerable pain). On this scale, the mean value was 33.77 ± 26.84 (s.d.) mm with a median of 30 (range: 0 to 100). Pain was rated as more than 50 mm in 319 cases (27.6%). The histograms showed that 587 patients (50.78%) had pain rated as less than or equal to 30 mm (Figure 2).
Premedication: among the 1164 patients for whom the information is available, 4 (0.34%) received premedication.

Gastro-intestinal disorders (Table 28) (Appendix 12)

During the 3 hours after the first administration of misoprostol, nausea were reported in 406 women out of the 1163 having received misoprostol and for whom the information is available (34.91%). The intensity is detailed in Table 28.
Vomiting was reported in 213 cases (18.31%), of mild or moderate intensity in 88.26% of cases.
A total of 32 patients (6.94%) received treatment for nausea or vomiting (consisting of metoclopramide in the majority of cases).
An episode of diarrhoea was reported in 122 cases out of 1163 (10.49%). Treatment was necessary in two cases.

Clinical signs observed within two hours after the second dose of misoprostol

Pelvic pain (Table 29) (Appendix 13)

Five hundred and sixty-eight women (79.33%) experienced painful uterine contractions during this period. The intensity of these contractions was severe in 32.92% of cases and treatment was required in 118 cases (16.53%). The intensity of pain evaluated on the visual analogic scale was 37.4 mm ± 28.65 (s.d.) with a median of 37 (range: 0 to 100).
Three hundred and nineteen women (45.1%) had pain of less than or equal to 30 mm.

Gastro-intestinal disorders (Table 30) (Appendix 14)

Within two hours after the second administration of misoprostol, nausea were observed in 14.5% of women. The intensity was severe in 18.27% of cases. Forty-eight women vomited (6.69%).
The nausea and vomiting required treatment in 7 cases (5.74%).
Sixty-four cases of diarrhoea were observed (8.93% of women). Treatment was prescribed in 3 cases only.

Blood pressure and heart rate (Table 31) (Appendices 15 and 16)

Two measurements of blood pressure per patient were scheduled in the protocol: one hour after the first administration of misoprostol and at the end of the first monitoring period or at the end of the second monitoring period, depending on the dose of misoprostol administered.

Four patients had a fall in systolic blood pressure ≥ 30 mg Hg between the first hour following the first administration of misoprostol and the end of the first monitoring period (No. 120, No. 738, No. 754, No. 796).

Twelve other patients had a fall in systolic blood pressure ≥ 30 mm Hg (two of them > 30 mm Hg: patients No. 630 = -45 mm Hg and No. 699 = -50 mm Hg) between the first hour following the first administration of misoprostol and the end of the second monitoring period (Nos. 82, 88, 123, 164, 171, 416, 746, 766, 769, 770).

None of these patients was treated for this fall in systolic blood pressure and none of these cases was reported as an adverse effect. All these measurements were systematic and prescribed by the protocol.

The episodes of malaise, hypotension and syncope reported as side-effects gave rise to blood pressure measurements other than those mentioned in this table.

Adverse events other than those reported in the previous paragraphs (Tables 32.1, 32.2, 32.3, 33, 34, 35, 36) (Appendices 17, 18, 19, 20)

Of the 1194 patients evaluable for safety, 375 (31.4%) had at least one intercurrent symptom. These are listed in Table 32.1. A case by case analysis of the patients with an intercurrent symptom is given in Appendices 17, 18, 19, 20.

The intercurrent symptoms considered by the investigator to be possibly or probably related to mifepristone are listed in Table 32.2. The most commonly reported adverse effects were: pelvic pain (n = 68 - 23.6%), metrorrhagia (n = 34, 11.8%), anaemia (n = 30 - 10.4%) and headache (n = 23 - 8%).

Regarding the adverse effects considered by the investigator to be possibly or probably related to misoprostol, the following were observed: pelvic pain (n = 59, 24%), metrorrhagia (n = 33, 13.4%), anaemia (n = 30, 12.2%) and uterine spasms (n = 20, 8.1%) (Table 32.3).

Most of the cases of anaemia reported as adverse events were treated with oral iron supplements.

During the study 18 episodes of malaise, 7 of hypotension and 2 of syncope were observed:

- **During the monitoring period in the centre, 10 episodes of malaise** occurred, distributed as follows:

  . malaises of vagal origin (Nos. 24, 418, 472, 1077, 1119),
  . malaise of hypoglycaemic appearance, but not confirmed by laboratory findings (No. 122),
  . other forms of malaise having not required treatment (No. 641, 1095).
  . in two cases this malaise was accompanied by a fall in systolic blood pressure (No. 302, systolic B.P. = 60 and No. 348, systolic B.P. = 90) and were treated by infusion of RINGER's solution®.

- **Five cases of hypotension** were reported as adverse effects **during monitoring in the centre** (No. 1178: collapse to 75/40 mmHg accompanied by metrorrhagia treated by RINGER's solution®; No. 312: B.P. 80/50 mmHg accompanied by respiratory difficulty, treated by RINGER's solution®; No. 360: systolic B.P. 60 with malaise, treated with RINGER's solution®; No. 374: systolic B.P. 80 with malaise, no treatment; No. 949: systolic B.P. 90 well tolerated clinically, no treatment).

The twelve other episodes of malaise, hypotension or syncope occurred outside the hours of monitoring in the centre:

- 5 malaises with no precise aetiology and not treated (Nos. 214, 739, 853 malaise on D_2, 929, 959);
- 1 malaise attributed to spasmophilia (No. 420),
- 3 malaises accompanied by metrorrhagia (No. 492: hospitalisation on D_3 for malaise + metrorrhagia after discharge from the centre, treatment with RINGER's solution®; No. 911: hospitalisation on D_2 for metrorrhagia and hypotension of 80 mmHg; No. 1076: hospitalisation on D_3 for malaise + metrorrhagia during return home),
- 2 episodes of syncope (No. 1184: syncope occurring at home, no treatment; No. 1114: hospitalisation on D_{21} for metrorrhagia with loss of consciousness on the public highway),
- 1 hypotension treated with PRAXINOR® (No. 985).

Serious adverse events (Table 42)

Forty-one serious adverse events (according to the definition of the term given in paragraph 3.4.2) were reported in 41 patients and in the majority of cases were the subject of immediate notification to the national health authorities in accordance with French legislation.

All these adverse events were considered "serious" as they caused either prolongation of the surveillance period on D_3 beyond the hours scheduled after the first and second dose of misoprostol, or hospitalisation.

These 41 serious adverse events were distributed as follows:

- *metrorrhagia:* n = 21 (Nos. 132, 144, 347, 370, 378, 420, 472, 492, 911, 1100, 1114, 1189), of which 9 cases required a haemostatic surgical procedure (Nos. 63, 122, 333, 348, 532, 668, 980, 1076, 1178).

- *pelvic pain:* n = 5 (No. 188: hospitalised on D_4 for retention; painful spontaneous expulsion requiring TEMGESIC®; 222; 520; 670: hospitalised on D_9 for pelvic pain treated with DOLOSAL® (ovular retention in the cervix); 1104

- *pelvic pain with metrorrhagia:* n = 4 (Nos. 522, 526, 946, 1095)

- *endometritis:* n = 3 (Nos. 531, 698, 832)

- *anaemia:* n = 2 (Nos. 751, 880). Both cases of anaemia were discovered during the follow-up visit and required a transfusion.

- *hypotensive malaises:* n = 2 (Nos. 302 and 360). The monitoring period was prolonged in both cases because of malaise, with a fall in systolic blood pressure to 60.

- *ectopic pregnancy:* n = 1 (No. 1117, calculated age = 54 D.A.; no ultrasound scan at inclusion, βHCG level = 12000). This patient was hospitalised as an emergency 2 days after administration of the 3 misoprostol tablets for a ruptured ectopic pregnancy. She underwent a left salpingectomy and received a blood transfusion.

- *spontaneous abortion of a 2nd pregnancy:* n = 1 (No. 1116). This patient took 2 tablets of misoprostol and expelled in the centre. She began oral contraception with STEDIRIL which was discontinued after 5 days. The patient was hospitalised 6 weeks after administration of mifepristone for severe metrorrhagia; the pelvic ultrasound scan taken was normal and βHCG levels weakly positive. The diagnosis of a spontaneous abortion of a second pregnancy was elicited.

- *anxiety:* n = 1 (No. 385). The surveillance period in the centre was prolonged in order to reassure the patient.

- *excision of a skin naevus:* n = 1 (No. 268).

10. DISCUSSION AND CONCLUSION

Efficacy

The aim of this multicentre study was to evaluate the efficacy and safety of a single dose of 600 mg of mifepristone in combination with 2 tablets (or 3 if there was no expulsion within 3 hours) of 200 μg of misoprostol, administered 36 to 48 hours later, for the termination of pregnancies of less than or equal to 63 days of amenorrhoea.

Of the 1195 patients included, 87 women were excluded from the analysis of efficacy, the majority of whom (n = 82), having expelled in the centre, did not return for the visit on D_{10} - D_{18}. Only 13 patients were actually lost to follow-up (they took misoprostol on D_3, did not expel at the centre and did not return for the follow-up visit). The analysis of efficacy therefore involved 1108 women (92.7%), which represents a satisfactory percentage.

Efficacy and gestational age

The percentage of successes was 92.87% (95% confidence interval = 91.2 - 94.3%). This percentage, which was 97.6% for pregnancies of less than 42 days of amenorrhoea, decreased progressively as the gestational age increased (86.8% for pregnancies of between 56 and 63 days of amenorrhoea). The reduction was more marked after 56 days (93.4% from 50 to 56 days and 86.8% from 57 to 63 days of amenorrhoea).

At the same time, an increase in the percentage of failures was observed: 1.6% of incomplete expulsions, 0.8% of ongoing pregnancies and 0% of haemostatic surgical procedures for pregnancies of less than 42 days compared to 5.5% of incomplete expulsions, 5.1% of ongoing pregnancies, 2.6% of haemostatic procedures for a gestational age of between 57 and 63 days of amenorrhoea.

The success and failure rates in this study were compared with those of the previous study (3) in 1286 women receiving a single dose of 600 mg of mifepristone in combination with 2 tablets of 200 μg of misoprostol administered 36 to 48 hours later for termination of pregnancies of less than or equal to 49 days of amenorrhoea (Table 38).

The results presented in Table 38 show, firstly, that the percentage of successes was reduced in the second study and, secondly, that the percentages of failures were all appreciably increased.

Efficacy and dose of misoprostol

More than half the patients (n = 718, 61.6%) who did not expel during the 3 hours of surveillance after administration of the two tablets of misoprostol received the third tablet.

It was noted that the success rate in the women having received 600 μg of misoprostol was less than that in the women having received 400 μg of misoprostol (90.3% versus 97%). This paradoxical observation may be explained by the fact that it was the women in whom expulsion was the most difficult who received the highest dose of misoprostol.

The percentage of women having taken 600 μg of misoprostol increased significantly (p = 0.0062) with gestational age: 60.2% for pregnancies of less than 42 days of amenorrhoea, 69.8% for a gestational age of between 57 and 63 days. In fact, the greater the gestational age, the more difficult the pregnancy termination and hence the more common the use of the third tablet of misoprostol.

In order to evaluate the benefit of the additional dose of misoprostol (200 μg), a comparison was made between the subgroup of women in this series with a gestational age of less than or equal to 49 days and who received 2 or 3 tablets of misoprostol (n = 465) and the whole population of the previous study (FFR/91/486/14) involving 1286 women (1208 women evaluable for efficacy).

The success and failure rates were similar in these two groups (Table 39). Administration of a third tablet of misoprostol did not therefore appear to improve the overall percentage of successes.

By carrying out the same comparison between these two populations for the percentage of early expulsions (before or during surveillance at the centre) and the percentage of expulsions within 72 hours after administration of mifepristone (Table 40), a slight increase was observed in the early expulsions in the recent study. However, the surveillance period had been extended by an additional hour compared with the previous study when a third tablet of misoprostol was administered (5 hours in total instead of 4 hours in the previous study), which may perhaps in part explain the increase in expulsion rate in the centre in the second study.

Safety

Almost all the patients had uterine bleeding.
The mean variation in haemoglobin level between D_1 and the follow-up visit was -0.8 g/dl ± 1.1 (range [redacted]). This figure was similar to that obtained in the previous study. Only four patients had a loss of between 5 and 7 g/dl of haemoglobin.

Three patients were transfused: one patient having undergone surgery for a ruptured ectopic pregnancy and two patients diagnosed as having anaemia at the scheduled follow-up visit between D_{10} and D_{18}.

Ten patients required a haemostatic surgical procedure. The percentage of these endo-uterine procedures increased with gestational age (0 for pregnancies of less than 42 days of amenorrhoea and 2.6% for a gestational age of between 57 and 63 days of amenorrhoea).

Abdominal pain was reported in 80.5% of women after the first administration of misoprostol and 79.3% after the second administration (81.5% of women had suffered from pain in the previous study).

The other adverse events reported were similar to those described in other studies.

Among the serious adverse events, mention should be made of the problem posed by the patient who underwent surgery for an ectopic pregnancy not diagnosed at inclusion (salpingectomy + transfusion). It should be noted that this patient had a relatively low βHCG level in relation to the calculated gestational age (βHCG = 12000 IU for a calculated age of 54 D.A.), which might have raised the suspicion of this diagnosis, and moreover that there was no ultrasound scan at inclusion. This confirms, firstly, that mifepristone is not a safe treatment for ectopic pregnancy and, secondly, that it is important to eliminate the diagnosis of ectopic pregnancy by all possible means before a medical termination of pregnancy.

Conclusion

The results of this study in 1195 patients confirm that administration of mifepristone (600 mg in a single dose) followed by that of misoprostol (400 or 600 μg) 36 to 48 hours later is highly effective and well tolerated for terminations of pregnancy of less than or equal to 49 days of amenorrhoea.

After 49 days, the efficacy of this combination decreases markedly as the gestational age increases.

The percentage of ongoing pregnancies, haemostatic endo-uterine procedures and incomplete expulsions increases in parallel.

This method is therefore not recommended for pregnancies of more than 49 days of amenorrhoea.

Regarding the dose of misoprostol, the addition of a third tablet if expulsion has not occurred after 3 hours is well tolerated and slightly improves the rate of early expulsions, but without increasing the overall success rate.

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Number of Pages (including this sheet):	12
Send to Facsimile Number:	9-1-301-443-9282
Date:	14 July 1996
Send to Company:	FDA, Division of Reproductive and Urologic Drug Products
Send to Person:	[redacted]
Subject:	U.S. Safety Data

Dear [redacted]

As requested during our teleconference call of 10 July 1996, attached please find a summary report of the serious adverse events (SAE) from Population Council Protocol 166A/B that have been reported to the FDA. The tables provide a listing of all subjects who experienced a serious adverse event during the U.S. trial, as well as the location of each reported SAE in the Population Council's IND [redacted] and NDA 20-687. This summary was generated solely for Council use in preparation for the upcoming July 19 advisory committee meeting. There is no new information in this summary that the agency has not received from us previously in the IND, NDA or NDA safety update--it is just presented in a different format and organization here. However, if you would like me to officially amend our IND and/or NDA with this summary, please inform me of this and I will do so.

I hope this information is helpful for you and other members of your division. Please contact me if you have further questions.

Best regards,

Ann Robbins, Ph.D.
Scientist

/S/ 7/24/96

cc:S. Arnold

RECD
HFD-510

MIF 004853

SUMMARY OF SERIOUS ADVERSE EVENTS REPORTED IN PROTOCOL 166A/B

Introduction

This internal Population Council report was generated in preparation for the upcoming Mifepristone NDA 20-687 advisory committee meeting on July 19, 1996. The goal was to summarize all serious adverse events (SAEs) that occurred during the conduct of Protocol 166A/B. SAEs are defined as those events reported to the Council from the clinics which the Council then reported to the FDA on Medwatch forms. All of these SAEs reports have been previously submitted to the FDA in IND —— as well as documented in NDA 20-687.

Results

The data relevant to SAEs have been summarized in the following three tables. Table 1 lists each participating clinic by clinic number, principal investigator name, location and type of clinic. Table 2 identifies, in chronological order of occurrence, each subject for whom a SAE was reported to the FDA on a Medwatch form. The nature of the adverse event(s) is recorded as well as the need for a dilatation and curettage (D&C) or aspiration, intravenous fluids, transfusion or hospitalization. When available, the subject's duration of amenorrhea and ethnicity is provided. Finally, the IND submission number and date the Medwatch form was submitted to the IND are listed.

The summary of Table 2 indicates that a total of 52 subjects had at least one SAE. There was more than one adverse event reported for most subjects on the Medwatch forms. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least 4 subjects are listed in the Summary of Table 2.

These serious adverse events resulted in the hospitalization of 26 subjects. Four subjects received transfusions. A total of 28 subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of 34 subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen (15) subjects received methergine or oxytocin for treatment of bleeding, although 11 of these subjects eventually had a surgical procedure.

The Drug Surveillance Department of Roussel Uclaf maintains a database of all serious adverse events associated with mifepristone for any medical use. At the request of Roussel, the Council sends to them information on all SAEs from the U.S. clinical trials that were reported to the FDA. Roussel assigns an "International Drug Surveillance Number" (IDSN) to each SAE and then provides a medical code for the reported SAE. These SAEs from the U.S. trial are thus captured in Roussel's database and are included in their quarterly reports of international SAEsa associated with mifepristone use. The SAEs from the Council's U.S. study have been reported in the NDA by this IDSN, in order to correspond to the report numbering system of other SAEs included in our NDA from international use of mifepristone in clinical trials and during post-marketing surveillance. However, this has caused some confusion in identification of subjects in the U.S. clinical trial for three reasons: 1) one subject may be assigned more than one IDSN by Roussel, depending upon how many adverse events occurred, since the IDSN is associated with an adverse event, not a subject; and 2) the medical code for the SAE assigned by Roussel may not precisely correspond to the description of the SAE as reported on the Medwatch form submitted to the FDA by the Council and 3) Roussel has made some mistakes in their coding of subject's identification. The purpose of Table 3 is to clarify the relationship between a subject in the U.S. trial and the IDSN(s) assigned to that subject by Roussel. In Table 3, each subject with an SAE in the Council's trial is identified and the IDSN(s), as assigned by Roussel, that are associated with that subject are listed. The medical code assigned by Roussel for the SAE(s) of each subject is also included.

For four subjects in the U.S. trial, Roussel has not yet assigned an IDSN or medical code (subject 123, clinic 01; subject 076, clinic 03; subject 070, clinic 02; and subject 159, clinic 01). The location in the NDA of the line listing of the SAE, as identified by the IDSN, is also indicated on Table 3. Line listings of all of the SAEs in the U.S. clinical trial were included in either the original NDA submission of March 14, 1996 (Volume 1.66, p. 32) or the NDA Safety Update Report of June 20, 1996 (Volume 3.2, p. 10).

Comparison of U.S. trials and pivotal NDA trials

It is not possible to make a complete comparison of the serious adverse events reported in the U.S. trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the U.S. trials has not been conducted, since the good clinical practice audit of the clinics is currently being completed. Therefore, at this time comparisons between the U.S. and NDA pivotal studies can only be made with the serious adverse events reported from these 52 U.S. subjects who had a Medwatch report, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire U.S. database. However, some general comparisons can be made. The total number of subjects enrolled in U.S. Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the U.S. trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by 41 subjects in the U.S. studies who required a Medwatch report. In the NDA pivotal studies, 52 subjects reported metorrhagia or excessive bleeding, which was categorized as severe in 21 subjects. However, the manner in which the bleeding was treated differed in the two studies. In the U.S. trials, 32 of the 34 surgical interventions (D&C or aspiration) reported on the Medwatch forms were performed on subjects experiencing hemorrhage. In the NDA pivotal trials, a total of 15 subjects

received surgical interventions for bleeding. The greater number of surgical interventions by U.S. investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the U.S., but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The U.S. investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were 5 cases of hypotension reported on Medwatch forms, although blood pressure readings were given for only 2 of these subjects. There were 7 cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia on the Medwatch forms for U.S. subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported on Medwatch forms of the U.S. subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the U.S. database.

Conclusions

The SAEs reported during the U.S. trial do not appear to differ significantly from those reported in the pivotal NDA trials, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the U.S. trials may be explained by the initial inexperience of U.S. clinicians in providing medical abortion. Investigators in the U.S. trial have indicated that there was a learning curve associated with the treatment of bleeding during the trial. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies. In summary, the current comparison of SAEs between our U.S. trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of U.S. settings.

Table 1

Clinics in Population Council U.S. Studies Protocol 166A/B

Clinic Number	Investigator Name	Location	Type of Clinic*	Protocol A or B
01	Mishell	Los Angeles, CA	University Hospital	A
02	Haskell	Des Moines, IA	Planned Parenthood	A
03	Poppema	Seattle, WA	Other	A
04	Tyson	Burlington, VT	Planned Parenthood	A
05	Blumenthal	Baltimore, MD	University Hospital	A
06	Borgotta	White Plains, NY	Planned Parenthood	A
07	Malloy	Atlanta, GA	Other	A
08	Rothenberg	Shrewsburg, NJ	Planned Parenthood	A
21	Poindexter	Houston, TX	Planned Parenthood	B
22	Vargas	Denver, CO	Planned Parenthood	B
23	[redacted]	[redacted]	[redacted]	B
24	Westhoff	New York, NY	University Hospital	B
25	Nichols	Portland, OR	Other	B
26	Sheehan	San Diego, CA	Planned Parenthood	B
27	Dean	St. Louis, MO	Other	B
28	Creinin	Pittsburgh, PA	University Hospital	B
29	Sogor	Cleveland, OH	Other	B

* Other = Clinic or Private Office.

Table 2

IND Safety Reports (Med Watch) Submitted to IND ——

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
(005)	22	Hemorrhage	X		X	X	X	63		107 11/21/94
036	02	Hemorrhage Vomiting Fainting	X		X			44		108 12/01/94
033	02	Vomiting Diarrhea Dehydration			X			49		108 12/01/94
027	02	Hemorrhage Cramping	X			X	X	53	East Asian	109 12/07/94
042	02	Hemorrhage Cramping Dizziness	X		X		X	51	Cau-casian	109 12/07/94
(057)	01	Hemorrhage Dizziness Headache Hypotension (BP 88/55, pulse 101) Tachycardia	X		X	X		44		110 12/20/94
015	25	Hemorrhage Cramping	X+					46		113 01/18/95
012	25	Hemorrhage Cramping	X					49		113 01/18/95
061	01	Hemorrhage Weak Nausea Pale & Cold			X			57		113 01/18/95
076	02	Hemorrhage Vomiting Cramping Chlamydial infection								113 01/18/95
033	03	Hemorrhage Syncope Pallor	X	X				52		113 01/18/95
022	25	Hemorrhage Cramping Feeling Faint	X		X		X	56		114 01/23/95
050	03	Hemorrhage Dizziness Postural Hypotension (BP 60/ palpable)	X				X	30		114 01/23/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
009	26	Hemorrhage Cramping Syncope	X		X		X	57		115 02/07/95
062	01	Hemorrhage Cramping	X				X	57	His-panic	118 02/15/95
107	01	Vomiting Dizziness			X					118 02/15/95
114	01	Hemorrhage	X	X			X	62	His-panic	118 02/15/95
123	01	Hemorrhage Dizziness Headache		X	X			53		118 02/15/95
037	04	Hemorrhage	X		X			65		118 02/15/95
109	01	Hemorrhage Fever	X		X		X	45		119 02/17/95
116	01	Chest Pain					X			119 02/17/95
048	03	Hemorrhage Tachycardia	X				X	51		120 03/03/95
076	03	Hemorrhage Cramping		X						121 03/06/95
060	24	Hemorrhage Hypotension Tachycardia			X	X		54		122 03/10/95
017	23	Hemorrhage Orthostatic Hypotension	X	X	X			57		123 03/13/95
070	02	Gunshot					X			123 03/13/95
030	23	Hemorrhage Syncope Tachycardia Hypotension	X		X			52		124 04/11/95
032	23	Vasovagal reaction			X					124 04/11/95
035	23	Hemorrhage		X	X					124 04/11/95
037	23	Hemorrhage Dizziness Shortness of Breath	X	X	X			51		124 04/11/95
081	26	Hemorrhage Syncope/neck injury	X+				X	51		124 04/11/95
158	02	Hemorrhage Weakness	X	X	X			54		125 04/19/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
159	01	Hemorrhage	X+	X	X			50		125 04/19/95
036	27	Pneumonia					X			132 06/07/95
012	29	Hemorrhage Cramping Faintness	X				X	53		132 06/07/95
028	04	Hemorrhage Dizziness		X						132 06/07/95
075	04	Nausea Dizziness			X					132 06/07/95
004	28	Hemorrhage	X	X			X	55		132 06/07/95
027	28	Hemorrhage Vomiting Lightheaded	X		X		X	50		133 06/13/95
071	23	Hemorrhage Vomiting Dizziness	X		X		X	55	Afro-Amer-ican	136 07/18/95
030	28	Hemorrhage								136 07/18/95
033	28	Hemorrhage	X				X	46		138 07/25/95
063	28	Anxiety attack Depression Threatened suicide					X	50		139 07/28/95
147	27	Viral meningitis					X			141 08/04/95
074	28	Hemorrhage Passed out	X	X	X		X	60		143 08/09/95
088	28	Hemorrhage (2 Med Watch reports)	X	X	X		X	62		143 08/09/95 144 08/10/95
018	07	Abdominal pain	X					42		145 08/15/95
019	07	Hemorrhage								145 08/15/95
104	28	Hemorrhage Cramping	X	X	X		X	62		146 08/25/95
108	28	Cramping Fever, tender uterus	X	X			X	63		147 09/01/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
116	24	Hemorrhagia Cramping Fever Endometritis	X		X			61		149 09/21/95
165	25	Hemorrhage Dizziness	X		X		X	60		154 11/02/95

Summary of Table 2

Total No. of Patients	Total No. of Clinics	Total No. of Adverse Events	Total Number of Treatments				Total No. Hospitalized
			D&C/ Asp.	Meth./ oxy.	IV Fluids	Transfusion	
52	13	**Hemorrhage 41** **Faint/Dizziness** 20** **Cramping 14** **Vomiting 06** **Hypotension 05** **Tachycardia 04**	34	15	28	04	26

* Listed in chronological order as reported to the FDA.
+ Surgical procedure not reported on Med Watch form.
D&C/Asp = Dilatation and Curettage/Aspiration.
Meth/oxy = Methergine/Oxytocin.
Hosp. = Hospitalizations.
DA = Number of days of amenorrhea.
** includes fainting, feeling faint or lightheaded, dizziness, vasovagal reaction, syncope and passing out.

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Table 3

Correlation between Population Council Subject and Serious Adverse Event Coded by Roussel

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
005)	22	199500076RU	Metrorrhagia Anemia	Vol. 1.66 p.32
		199500439RU	Metrorrhagia Abdominal pain	Vol. 3.2 p.10
036	02	199500072RU	Metrohagia Vomiting Malaise	Vol. 1.66 p.32
033	02	199500442RU	Dehydration Nausea Vomiting Diarrhea	Vol. 3.2 p.10
027	02	199500074RU	Abdominal pain Anemia Metrorrhagia	Vol. 1.66 p.32
042	02	199500075RU	Abdominal pain Metrorrhagia Anemia	Vol. 1.66 p.32
(057)	01	199500071RU	Metrorrhagia Hypotension Anemia	Vol. 1.66 p.32
		199500440RU	Metrorrhagia Hypotension Headache	Vol. 3.2 p.10
015	25	199500066RU	Metrorrhagia	Vol. 1.66 p.32
012	25	199500067RU	Metrorrhagia	Vol. 1.66 p.32
061	01	199500068RU	Hypotension	Vol. 1.66 p.32
076	02	199500069RU	Urogenital Disorder	Vol. 1.66 p.32
033	03	199500070RU	Metrorrhagia Syncope	Vol. 1.66 p.32
		199500444RU	Metrorrhagia Dizziness Headache	Vol. 3.2 p.10
022	25	199500441RU	Abdominal Pain Hypotension	Vol. 3.2 p.10
		199500064RU	Metrorrhagia	Vol. 1.66 p.32

Table 3 (Cont'd)

Patient No.	Clinic No.	IDSN*	SA** Coded by Roussel	Location in NDA Volume Page
050	03	199500065RU	Metrorrhagia Postural hypotension	Vol. 1.66 p.32
009	26	199500077RU	Metrorrhagia	Vol. 1.66 p32
062	01	199500102RU	Metrorrhagia	Vol. 1.66 p.32
107	01	199500443RU	Vomiting Nausea Dizziness	Vol. 3.2 p.10
114	01	199500104RU	Metrorrhagia	Vol. 1.66 p.32
123	01	NA***	NA	Vol. 1.66 p.32
037	04	199500106RU	Metrorrhagia	Vol. 1.66 p.32
109	01	199500100RU	Metrorrhagia Fever	Vol. 1.66 p32
116	01	199500101RU	Chest pain	Vol. 1.66 p.32
048	03	199500140RU	Metrorrhagia	Vol. 1.66 p.32
076	03	NA	NA	Vol. 1.66 p.32
060	24	199500139RU	Metrorrhagia Hypotension	Vol. 1.66 p.32
017	23	199500135RU	Metrorrhagia Postural Hypotension	Vol. 1.66 p.32
070	02	NA	NA	Vol. 1.66 p.32
030	23	199500175RU	Metrorrhagia Syncope	Vol. 1.66 p.32
032	23	199500446RU	Syncope	Vol. 3.2 p.10
035	23	199500447RU	Metrorrhagia	Vol. 3.2 p.10
037	23	199500176RU	Metrorrhagia	Vol. 1.66 p.32
081	26	199500172RU	Metrorrhagia Syncope	Vol. 1.66 p.32
158	02	199500179RU	Metrorrhagia	Vol. 1.66 p.32
159	01	NA	NA	Vol. 1.66 p.32
036	27	199500247RU	Pneumonia	Vol. 1.66 p.32

Table 3 (Cont'd)

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
012	29	199500248RU	Metrorrhagia	Vol. 1.66 p.32
028	04	199500249RU	Metrorrhagia	Vol. 1.66 p.32
075	04	199500448RU	Dehydration	Vol. 3.2 p.10
004	28	199500251RU	Metrorrhagia	Vol. 1.66 p.32
027	28	199500455RU	Metrorrhagia	Vol. 3.2 p.10
071	23	199500329RU 199500449	Vomiting Metrorrhagia Dizziness	Vol. 1.66 p.32 Vol. 1.66 p.32
030	28	199500330RU	Metrorrhagia	Vol. 1.66 p.32
033	28	199500454RU	Metrorrhagia	Vol. 1.66 p.32
063	28	199500340RU	Depression	Vol. 1.66 p.32
147	27	199500342RU	Meningitis	Vol. 3.2 p.10
074	28	199500450RU 199500355RU	Metrorrhagia Hypotension Metrorrhagia Hypotension Anemia	Vol. 3.2 p10 Vol. 3.2 p.10
088	28	199500356RU 199500451RU	Metrorrhagia Metrorrhagia	Vol. 3.2 p.10 Vol. 3.2 p.10
018	07	199500365RU	Abdominal pain	Vol. 3.2 p.10
019	07	199500366RU	Metrorrhagia	Vol. 3.2 p.10
104	28	199500452RU	Metrorrhagia Uterine spasm	Vol. 3.2 p.10
108	28	199500375RU	Abdominal pain Fever	Vol. 3.2 p.10
116	24	199500453RU	Metrorrhagia Endometrial disorder	Vol. 3.2 p.10
165	25	199500427RU	Metrorrhagia Malaise	Vol. 3.2 p.10

*IDSN= International Drug Surveillance Number.
**SAE = Serious Adverse Event.
***NA = Not available, not yet assigned by Roussel.

The Population Council

Center for
omedical Research -

dated 6/18/98 /S/

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N 163 I M IC

1230 York Avenue
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Cable: Popblomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

April 19, 1996

By FedEx

/S/ 5/1/98

dated

/S/ 4-30

—— Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Document Control Room 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: IND —— Mifepristone Tablets, 200 mg
Submission Serial Number: 162
Information Amendment - Clinical
- Chemistry, Manufacturing and Controls

Dear ——

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to amend our application with new information, as follows:

1. **Clinical Information**
Attachment I contains a periodic safety update report received from the product manufacturer. The report covers the period from January 1, 1996 through March 31, 1996.

2. **Chemistry, Manufacturing and Control Information**
On page 229 of a previous amendment to this IND (Submission Serial Number 158/March 8, 1996), information was included from the product manufacturer to discuss the reasons for selection of —— as the starting material in the synthesis of mifepristone. In that discussion, the manufacturer noted that different multiple step syntheses of —— are published in three patents:

Copies of these patents have now been obtained and are included in Attachments II, III and IV, respectively. Also, a copy of an English translation of the Chinese Patent is included in Attachment II.

Please contact me should there be any questions or comments regarding the above information.

Sincerely yours,

Ann Robbins, Ph.D.
Scientist

Attachments: Described above.

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REVIEWS COMPLETED
CSO ACTION:
ISL
CSO INITIALS
DATE

The Population Council

Center for
Medical Research

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March 25, 1996

BY FEDEX

/S/ 5/17/96

CENTER FOR DRUG
REC'D
MAR 26 1996
HFD-510
EVALUATION AND RESEARCH

REVIEWS COMPLETED
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/S/ 5/17/96
INITIALS DATE

Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Document Control Room 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: IND — Mifepristone Tablets, 200 mg
Submission Serial Number: 160
General Correspondence: Request for Exemption from Imprinting of Solid Dosage Form

noted
/S/
Sponsor should be informed that 21CFR 206 exempts drug products for clinical investigation from the imprint requirements. However TREATMENT IN are not exempted
/S/
5/16/96

Dear —

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion. With this submission, we wish to request an exemption from the requirement for the imprinting of solid oral dosage forms which would permit us to provide our remaining supply of mifepristone tablets for use in other independent treatment and research programs.

We presently have available a residual supply of approximately — mifepristone tablets which was provided in 1994 by the manufacturer, Roussel Uclaf, for our investigational clinical studies in this country. These tablets have an expiration date of July 1997 and do not bear imprinting as is required by CFR Part 206 which became effective in September 1995. We anticipate that no further drug supplies will be provided by the manufacturer.

Our clinical studies with the drug were completed last year and it has been our intention to use the remaining supply of the drug as a source of material for treatment and academic research INDs sponsored by other parties. It is our understanding that in the absence of an exemption by the agency, the new regulation requiring imprinting of tablets will prohibit this use of the drug supply. We thus would appreciate your granting an exemption from the regulation to permit us to provide the remaining supply of the drug for use in investigational studies approved by the agency.

A related authorization to cross-reference our IND in support of a study — which we have also been requested to provide drug supplies is being forwarded separately in Serial Submission 161.

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Please contact me should there be any questions or comments regarding our request.

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

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The Population Council

Center for
Biomedical Research

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/S/ 10/9/96

/S/ 11-__-97

/S/ 11/10/97

30 September 1996

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 10/__/97
CSO INITIALS DATE

Division of Reproductive and
Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 170
Annual Report

Dear ———

We refer to our above Investigational New Drug Application (IND) which provides for clinical studies with mifepristone in the induction of abortion.

Please find enclosed our annual report which describes recent activities in the development program with mifepristone. The cut-off date for this report is July 31, 1996 and the document covers the period of time since the July 31, 1995 cut-off date for our last annual report (Submission 150) which was submitted on September 26, 1995.

In the time period covered by this report, we also submitted NDA 20-687 and several subsequent amendments to that NDA which provides for the use of mifepristone in the induction of abortion. We ask that these NDA submissions be incorporated by reference in this IND.

Please contact me should there be any questions or comments regarding this submission.

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

Enclosure

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RECD OCT 1 1996 HFD-580

MIF 004870

SUMMARY OF SERIOUS ADVERSE EVENTS REPORTED IN PROTOCOL 166A/B

Introduction

This is a summary of all serious adverse events (SAEs) that occurred during the conduct of Protocol 166A/B, the U.S. clinical trial on the use of mifepristone and misoprostol for the termination of early pregnancy. SAEs are defined as those events reported to The Population Council from the participating clinics which the Council then reported to the FDA on Medwatch forms. All of these SAE reports have been previously submitted to the FDA in IND —— as well as documented in NDA 20-687. Parts of this summary of SAEs from the U.S. trial were presented at the Reproductive Health Drugs advisory committee meeting held on July 19, 1996 for Mifepristone NDA 20-687.

Results

The data relevant to SAEs have been summarized in the following four tables. Table 1 lists each participating clinic by clinic number, principal investigator name, location and type of clinic. Table 2 identifies, in chronological order of occurrence, each subject for whom a SAE was reported to the FDA on a Medwatch form. The nature of the adverse event(s) is recorded as well as the need for a dilatation and curettage (D&C) or aspiration, intravenous fluids, transfusion or hospitalization. When available, the subject's duration of amenorrhea and ethnicity is provided. Finally, the IND submission number and date the Medwatch form was submitted to the IND are listed.

The summary of Table 2 indicates that a total of 52 subjects had at least one SAE. There was more than one adverse event reported for most subjects on the Medwatch forms. The most frequently reported SAE was hemorrhage (41 reports). This was followed by fainting/dizziness (20 reports) which includes all of the following events: fainting, feeling faint or lightheaded, dizziness, syncope, vasovagal reaction and passing out. Other serious adverse events that were reported by at least 4 subjects are listed in the Summary of Table 2.

These serious adverse events resulted in the hospitalization of 26 subjects. Four subjects received transfusions. A total of 28 subjects received IV fluids (including 3 of the subjects that also had transfusions). A total of 34 subjects received a D&C or aspiration. All but two of the subjects who had a D&C or aspiration reported hemorrhage. Fifteen (15) subjects received methergine or oxytocin for treatment of bleeding, although 11 of these subjects eventually had a surgical procedure.

The Drug Surveillance Department of Roussel Uclaf maintains a database of all serious adverse events associated with mifepristone for any medical use. At the request of Roussel, the Council sends to them information on all SAEs from the U.S. clinical trials that were reported to the FDA. Roussel assigns an "International Drug Surveillance Number" (IDSN) to each SAE and then provides a medical code for the reported SAE. These SAEs from the U.S. trial are thus captured in Roussel's database and are included in their quarterly reports of international SAEs associated with mifepristone use. The SAEs from the Council's U.S. study have been reported in the NDA by this IDSN, in order to correspond to the report numbering system of other SAEs included in our NDA from international use of mifepristone in clinical trials and during post-marketing surveillance. However, this has caused some confusion in identification of subjects in the U.S. clinical trial for three reasons: 1) one subject may be assigned more than one IDSN by Roussel, depending upon how many adverse events occurred, since the IDSN is associated with an adverse event, not a subject; and 2) the medical code for the SAE assigned by Roussel may not precisely correspond to the description of the SAE as reported on the Medwatch form submitted to the FDA by the Council and 3) Roussel has made some mistakes in their coding of subject's identification. The purpose of Table 3 is to clarify the relationship between a subject in the U.S. trial and the IDSN(s) assigned to that subject by Roussel. In Table 3, each subject with an SAE in the Council's trial is identified and the IDSN(s), as assigned by Roussel, that are associated with that subject are listed. The medical code assigned by Roussel for the SAE(s) of each subject is also included.

For four subjects in the U.S. trial, Roussel has not yet assigned an IDSN or medical code (subject 123, clinic 01; subject 076, clinic 03; subject 070, clinic 02; and subject 159, clinic 01). The location in the NDA of the line listing of the SAE, as identified by the IDSN, is also indicated on Table 3. Line listings of all of the SAEs in the U.S. clinical trial were included in either the original NDA submission of March 14, 1996 (Volume 1.66, p. 32) or the NDA Safety Update Report of June 20, 1996 (Volume 3.2, p. 10).

Comparison of U.S. trials and pivotal NDA trials

It is not possible to make a complete comparison of the serious adverse events reported in the U.S. trial and the pivotal French studies in the NDA, due to different definitions of SAEs and different adverse event reporting requirements in the two countries. Also, the safety analysis of the U.S. trials has not been conducted, since the good clinical practice audit of the clinics has just been completed. Therefore, at this time comparisons between the U.S. and NDA pivotal studies can only be made with the serious adverse events reported from these 52 U.S. subjects who had a Medwatch report, rather than other less serious adverse events that will be uncovered during the safety analysis of the entire U.S. database. However, some general comparisons can be made, as summarized in Table 4. The total number of subjects enrolled in U.S. Protocol 166A/B was 2,121. This is slightly less than the number of subjects (2480) enrolled in the pivotal French trials in the NDA. The number of transfusions is identical (4) in both studies and the number of hospitalizations is similar (26 in the U.S. trials and 21 in the pivotal trials). The number of reported cases of hemorrhage, metorrhagia or excessive bleeding was similar in the two studies. Hemorrhage was reported by 41 subjects in the U.S. studies who required a Medwatch report. In the NDA pivotal studies, 52 subjects reported metorrhagia or excessive bleeding, which was categorized as severe in 21 subjects. However, the manner in which the bleeding was treated differed in the two studies. In the U.S. trials, 32 of the 34 surgical interventions (D&C or aspiration) reported on the Medwatch forms were performed on subjects experiencing hemorrhage. In the NDA

pivotal trials, a total of 15 subjects received surgical interventions for bleeding. The greater number of surgical interventions by U.S. investigators is not unexpected, due to their initial lack of experience in the control of bleeding during medical abortion. This was the first clinical trial of medical abortion in the U.S., but medical abortion had been available in France for several years prior to the conduct of the French studies of mifepristone and misoprostol. The U.S. investigators have noted that as they gained experience with the bleeding that occurs during medical abortion, they were less likely to surgically intervene.

There were 5 cases of hypotension reported on Medwatch forms, although blood pressure readings were given for only 2 of these subjects. There were 7 cases of clinically relevant hypotension, one rated as severe, in the NDA pivotal trials. There were also a similar number of reports of tachycardia on the Medwatch forms for U.S. subjects and in the pivotal trials (4 and 5 reports, respectively).

The incidence of other adverse events reported on Medwatch forms of the U.S. subjects, such as cramping or vomiting, cannot at this time be fairly compared to the numbers of these adverse events reported from all subjects in the NDA pivotal studies. This comparison must await the safety analysis of the U.S. database. These results will be submitted to the FDA as soon as the analysis is completed.

Conclusions

The SAEs reported during the U.S. trial do not appear to differ significantly from those reported in the pivotal NDA trials, although a full comparison is not possible at this time. The higher incidence of surgical intervention in the U.S. trials may be explained by the initial inexperience of U.S. clinicians in providing medical abortion. The incidence of other events such as hemorrhage, transfusions, and hospitalizations were similar in the two studies. In summary, the current comparison of SAEs between our U.S. trial and the NDA pivotal trials indicated that medical abortion can be safely delivered in a wide variety of U.S. settings.

Table 2

IND Safety Reports (Med Watch) Submitted to IND

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
(005)	22	Hemorrhage	X		X	X	X	63	Caucasian	107 11/21/94
036	02	Hemorrhage Vomiting Fainting	X		X			44	Caucasian	108 12/01/94
033	02	Vomiting Diarrhea Dehydration			X			49	Caucasian	108 12/01/94
027	02	Hemorrhage Cramping	X			X	X	53	East Asian	109 12/07/94
042	02	Hemorrhage Cramping Dizziness	X		X		X	51	Caucasian	109 12/07/94
(057)	01	Hemorrhage Dizziness Headache Hypotension (BP 88/55, pulse 101) Tachycardia	X		X	X		44	Caucasian	110 12/20/94
015	25	Hemorrhage Cramping	X+					46	Caucasian	113 01/18/95
012	25	Hemorrhage Cramping	X					49	Caucasian	113 01/18/95
061	01	Hemorrhage Weak Nausea Pale & Cold			X			57	Hispanic	113 01/18/95
076	02	Hemorrhage Vomiting Cramping Chlamydial infection							Hispanic/ American Indian	113 01/18/95
033	03	Hemorrhage Syncope-- Pallor	X	X				52	Caucasian	113 01/18/95
022	25	Hemorrhage Cramping Feeling Faint	X		X		X	56	Caucasian	114 01/23/95
050	03	Hemorrhage Dizziness Postural Hypotension (BP 60/ palpable)	X				X	30	Caucasian	114 01/23/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
009	26	Hemorrhage Cramping Syncope	X		X		X	57	Caucasian	115 02/07/95
062	01	Hemorrhage Cramping	X				X	57	Hispanic	118 02/15/95
107	01	Vomiting Dizziness			X				Caucasian	118 02/15/95
114	01	Hemorrhage	X	X			X	62	Hispanic	118 02/15/95
123	01	Hemorrhage Dizziness Headache		X	X			53	Hispanic	118 02/15/95
037	04	Hemorrhage	X		X			65	Caucasian	118 02/15/95
109	01	Hemorrhage Fever	X		X		X	45	Hispanic	118 02/17/95
116	01	Chest Pain					X		Caucasian	119 02/17/95
048	03	Hemorrhage Tachycardia	X				X	51	Caucasian	120 03/03/95
076	03	Hemorrhage Cramping		X					African-American	121 03/06/95
060	24	Hemorrhage Hypotension Tachycardia			X	X		54	Caucasian	122 03/10/95
017	23	Hemorrhage Orthostatic Hypotension	X	X	X			57	Caucasian	123 03/13/95
070	02	Gunshot					X		Caucasian	123 03/13/95
030	23	Hemorrhage Syncope Tachycardia Hypotension	X		X			52	Caucasian	124 04/11/95
032	23	Vasovagal reaction			X				Caucasian	124 04/11/95
035	23	Hemorrhage		X	X				East Asian	124 04/11/95
037	23	Hemorrhage Dizziness Shortness of Breath	X	X	X			51	African	124 04/11/95
081	26	Hemorrhage Syncope/neck injury	X+				X	51	Caucasian	124 04/11/95
158	02	Hemorrhage Weakness	X	X	X			54	Caucasian	125 04/19/95

Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
159	01	Hemorrhage	X+	X	X			50	Hispanic	125 04/19/95
036	27	Pneumonia					X		Caucasian	132 06/07/95
012	29	Hemorrhage Cramping Faintness	X				X	53	Caucasian	132 06/07/95
028	04	Hemorrhage Dizziness		X					Caucasian	132 06/07/95
075	04	Nausea Dizziness			X				Caucasian	132 06/07/95
004	28	Hemorrhage	X	X			X	55	African-American	132 06/07/95
027	28	Hemorrhage Vomiting Lightheaded	X		X		X	50	Caucasian	13[illegible] 06/1[illegible]95
071	23	Hemorrhage Vomiting Dizziness	X		X		X	55	African-American	136 07/18/95
030	28	Hemorrhage							African-American	136 07/18/95
033	28	Hemorrhage	X				X	46	African-American	138 07/25/95
063	28	Anxiety attack Depression Threatened suicide					X	50	Caucasian	139 07/28/95
147	27	Viral meningitis					X		Caucasian	141 08/04/95
074	28	Hemorrhage Passed out	X	X	X		X	60	Caucasian	143 08/09/95
088	28	Hemorrhage (2 Med Watch reports)	X	X	X		X	62	Caucasian	143 08/09/95 144 08/10/95
018	07	Abdominal pain	X					42	African-American	145 08/15/95
019	07	Hemorrhage							Caucasian	145 08/15/95
104	28	Hemorrhage Cramping	X	X	X		X	62	Caucasian	146 08/25/95
108	28	Cramping Fever, tender uterus	X	X			X	63	Caucasian	147 09/01/95

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Table 2 (Cont'd)

Patient No.	Clinic No.	Adverse Event	D&C/ Asp.	Meth./ oxy.	IV Fluids	Trans-fusion	Hosp.	DA	Race	IND No. and Date
116	24	Hemorrhagia Cramping Fever Endometritis	X		X			61	African-American	149 09/21/95
165	25	Hemorrhage Dizziness	X		X		X	60	Caucasian	154 11/02/95

Summary of Table 2

Total No. of Patients	Total No. of Clinics	Total No. of Adverse Events	Total Number of Treatments				Total No. Hospitalized
			D&C/ Asp.	Meth./ oxy.	IV Fluids	Transfusion	
52	13	**Hemorrhage 41** **Faint/Dizziness** 20** **Cramping 14** **Vomiting 06** **Hypotension 05** **Tachycardia 04**	34	15	28	04	26

* Listed in chronological order as reported to the FDA.
+ Surgical procedure not reported on Med Watch form.
D&C/Asp = Dilatation and Curettage/Aspiration.
Meth/oxy = Methergine/Oxytocin.
Hosp. = Hospitalizations.
DA = Number of days of amenorrhea.
** includes fainting, feeling faint or lightheaded, dizziness, vasovagal reaction, syncope and passing out.

Table 3

Correlation between Population Council Subject and Serious Adverse Event Coded by Roussel

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
(005)	22	199500076RU	Metrorrhagia Anemia	Vol. 1.66 p.32
		199500439RU	Metrorrhagia Abdominal pain	Vol. 3.2 p.10
036	02	199500072RU	Metrohagia Vomiting Malaise	Vol. 1.66 p.32
033	02	199500442RU	Dehydration Nausea Vomiting Diarrhea	Vol. 3.2 p.10
027	02	199500074RU	Abdominal pain Anemia Metrorrhagia	Vol. 1.66 p.32
042	02	199500075RU	Abdominal pain Metrorrhagia Anemia	Vol. 1.66 p.32
)57)	01	199500071RU	Metrorrhagia Hypotension Anemia	Vol. 1.66 p.32
		199500440RU	Metrorrhagia Hypotension Headache	Vol. 3.2 p.10
015	25	199500066RU	Metrorrhagia	Vol. 1.66 p.32
012	25	199500067RU	Metrorrhagia	Vol. 1.66 p.32
061	01	199500068RU	Hypotension	Vol. 1.66 p.32
076	02	199500069RU	Urogenital Disorder	Vol. 1.66 p.32
033	03	199500070RU	Metrorrhagia Syncope	Vol. 1.66 p.32
		199500444RU	Metrorrhagia Dizziness Headache	Vol. 3.2 p.10
022	25	199500441RU	Abdominal Pain Hypotension	Vol. 3.2 p.10
		199500064RU	Metrorrhagia	Vol. 1.66 p.32

Table 3 (Cont'd)

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
050	03	199500065RU	Metrorrhagia Postural hypotension	Vol. 1.66 p.32
009	26	199500077RU	Metrorrhagia	Vol. 1.66 p32
062	01	199500102RU	Metrorrhagia	Vol. 1.66 p.32
107	01	199500443RU	Vomiting Nausea Dizziness	Vol. 3.2 p.10
114	01	199500104RU	Metrorrhagia	Vol. 1.66 p.32
123	01	NA***	NA	Vol. 1.66 p.32
037	04	199500106RU	Metrorrhagia	Vol. 1.66 p.32
109	01	199500100RU	Metrorrhagia Fever	Vol. 1.66 p32
116	01	199500101RU	Chest pain	Vol. 1.66 p.32
048	03	199500140RU	Metrorrhagia	Vol. 1.66 p.32
076	03	NA	NA	Vol. 1.66 p.32
060	24	199500139RU	Metrorrhagia Hypotension	Vol. 1.66 p.32
017	23	199500135RU	Metrorrhagia Postural Hypotension	Vol. 1.66 p.32
070	02	NA	NA	Vol. 1.66 p.32
030	23	199500175RU	Metrorrhagia Syncope	Vol. 1.66 p.32
032	23	199500446RU	Syncope	Vol. 3.2 p.10
035	23	199500447RU	Metrorrhagia	Vol. 3.2 p.10
037	23	199500176RU	Metrorrhagia	Vol. 1.66 p.32
081	26	199500172RU	Metrorrhagia Syncope	Vol. 1.66 p.32
158	02	199500179RU	Metrorrhagia	Vol. 1.66 p.32
159	01	NA	NA	Vol. 1.66 p.32
036	27	199500247RU	Pneumonia	Vol. 1.66 p.32

Table 3 (Cont'd)

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
050	03	199500065RU	Metrorrhagia Postural hypotension	Vol. 1.66 p.32
009	26	199500077RU	Metrorrhagia	Vol. 1.66 p32
062	01	199500102RU	Metrorrhagia	Vol. 1.66 p.32
107	01	199500443RU	Vomiting Nausea Dizziness	Vol. 3.2 p.10
114	01	199500104RU	Metrorrhagia	Vol. 1.66 p.32
123	01	NA***	NA	Vol. 1.66 p.32
037	04	199500106RU	Metrorrhagia	Vol. 1.66 p.32
109	01	199500100RU	Metrorrhagia Fever	Vol. 1.66 p32
116	01	199500101RU	Chest pain	Vol. 1.66 p.32
048	03	199500140RU	Metrorrhagia	Vol. 1.66 p.32
076	03	NA	NA	Vol. 1.66 p.32
060	24	199500139RU	Metrorrhagia Hypotension	Vol. 1.66 p.32
017	23	199500135RU	Metrorrhagia Postural Hypotension	Vol. 1.66 p.32
070	02	NA	NA	Vol. 1.66 p.32
030	23	199500175RU	Metrorrhagia Syncope	Vol. 1.66 p.32
032	23	199500446RU	Syncope	Vol. 3.2 p.10
035	23	199500447RU	Metrorrhagia	Vol. 3.2 p.10
037	23	199500176RU	Metrorrhagia	Vol. 1.66 p.32
081	26	199500172RU	Metrorrhagia Syncope	Vol. 1.66 p.32
158	02	199500179RU	Metrorrhagia	Vol. 1.66 p.32
159	01	NA	NA	Vol. 1.66 p.32
036	27	199500247RU	Pneumonia	Vol. 1.66 p.32

Table 3 (Cont'd)

Patient No.	Clinic No.	IDSN*	SAE** Coded by Roussel	Location in NDA Volume Page
012	29	199500248RU	Metrorrhagia	Vol. 1.66 p.32
028	04	199500249RU	Metrorrhagia	Vol. 1.66 p.32
075	04	199500448RU	Dehydration	Vol. 3.2 p.10
004	28	199500251RU	Metrorrhagia	Vol. 1.66 p.32
027	28	199500455RU	Metrorrhagia	Vol. 3.2 p.10
071	23	199500329RU 199500449	Vomiting Metrorrhagia Dizziness	Vol. 1.66 p.32 Vol. 1.66 p.32
030	28	199500330RU	Metrorrhagia	Vol. 1.66 p.32
033	28	199500454RU	Metrorrhagia	Vol. 1.66 p.32
063	28	199500340RU	Depression	Vol. 1.66 p.32
147	27	199500342RU	Meningitis	Vol. 3.2 p.10
074	28	199500450RU 199500355RU	Metrorrhagia Hypotension Metrorrhagia Hypotension Anemia	Vol. 3.2 p10 Vol. 3.2 p.10
088	28	199500356RU 199500451RU	Metrorrhagia Metrorrhagia	Vol. 3.2 p.10 Vol. 3.2 p.10
018	07	199500365RU	Abdominal pain	Vol. 3.2 p.10
019	07	199500366RU	Metrorrhagia	Vol. 3.2 p.10
104	28	199500452RU	Metrorrhagia Uterine spasm	Vol. 3.2 p.10
108	28	199500375RU	Abdominal pain Fever	Vol. 3.2 p.10
116	24	199500453RU	Metrorrhagia Endometrial disorder	Vol. 3.2 p.10
165	25	199500427RU	Metrorrhagia Malaise	Vol. 3.2 p.10

*IDSN= International Drug Surveillance Number.
**SAE = Serious Adverse Event.
***NA = Not available, not yet assigned by Roussel.

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Table 4

Comparison of Serious Adverse Events (SAE)* in the U.S. Clinical Trial and NDA Pivotal Trials

	U.S.	French
No. subjects enrolled	2121	2480
No. of hospitalizations	26 (1%)	21 (1%)
No. of transfusions	4 (<1%)	4 (<1%)
No. of subjects with hemorrhage	41 (2%)	52 (2%)
Surgical intervention for bleeding	32 (2%)	15 (1%)

*reported on Medwatch form to the FDA

312.33 (b) Summary Information. Information obtained during the previous year's clinical and nonclinical investigations, including:

(2) A summary of all IND safety reports submitted during the past year.

The following table summarizes all IND safety reports submitted in association with the US clinical studies conducted under Protocols 166 A/B. The last page of the table summarizes safety reports submitted during the past year [in the period from the cut-off date of the last annual report (July 31, 1995) to the cut-off date for this report (July 31, 1996)].

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Protocol 166A/B - IND Safety Reports Submitted to the FDA

IND Submission (Number-Date)	Patient Identification/ International Drug Surveillance Number	Investigator and Clinic Number	Adverse Events Reported to FDA	Adverse Events as Reported by Roussel	Adverse Events as Coded by Roussel
107 - 11/21/94	C01(005)/199500076RU (same as 199500439RU, added mild cramping, Caucasian, 63 days amenorrhea, 26 yr old)	Vargas 22	Hemorrhage, D&C, IV fluids and 2 units of packed RBCs administered. History of post-partum hemorrhage (hospitalized)	Bleeding requiring curettage Anemia (Hb 5.6 g/dl), blood transfusion	Metrorrhagia Anemia Abdominal pain
108 - 12/01/94	036/199500072RU (Caucasian, 44 days amenorrhea, 20 yr old)	Haskell 02	Fainting, vomiting, dehydration, hemorrhage, nausea, aspiration performed and IV fluids administered	Severe bleeding Vomiting Fainting	Metrorrhagia Vomiting Malaise
	033/199500442RU (Caucasian, 49 days amenorrhea, 33 yr old)	Haskell 02	Nausea, dehydration, vomiting, diarrhea, IV fluids administered	Dehydration/IV fluids Nausea Vomiting Diarrhea	Dehydration Nausea Vomiting Diarrhea
109 - 12/07/94	027/199500074RU (East Asian, 53 days amenorrhea, 34 yr old)	Haskell 02	Severe cramping. Hemorrhage, D&C and 4 units of packed RBCs administered (hospitalized)	Severe cramping Anemia Heavy bleeding	Abdominal pain Anemia Metrorrhagia
	042/199500075RU (Caucasian, 51 days amenorrhea, 32 yr old)	Haskell 02	Severe cramping, dizziness, losing consciousness, hemorrhage, D&C. IV fluids administered (hospitalized)	Severe cramping Heavy bleeding/ curettage Anemia (Hb 6.5 gm/l) - no transfusion	Abdominal pain Metrorrhagia Anemia
110 - 12/20/94	057)/199500071RU (same as 199500440RU, added transfusion and headache, Caucasian, 44 days amenorrhea, 26 yr old)	Mishell 01	Dizziness, headache, hypotension, tachycardia, hemorrhage, suction curettage (D&C), 1 unit of blood and IV fluids administered	Bleeding Hypotension Anemia	Metrorrhagia Hypotension Anemia Headache

August 06 1996

Protocol 166A/B - IND Safety Reports Submitted to the FDA

IND Submission (Number-Date)	Patient Identification/ International Drug Surveillance Number	Investigator and Clinic Number	Adverse Events Reported to FDA	Adverse Events as Reported by Roussel	Adverse Events as Coded by Roussel
113 - 01/18/95	015/199500066RU (Caucasian, 46 days amenorrhea, 24 yr old)	Nichols 25	Hemorrhage and cramping (D&C not on Med Watch)	Heavy bleeding/D&C	Metrorrhagia
	012/199500067RU (Caucasian, 49 days amenorrhea, 25 yr old)	Nichols 25	Hemorrhage, cramping D&C	Heavy bleeding requiring curettage	Metrorrhagia
	061/199500068RU (Hispanic, 57 days amenorrhea, 30 yr old)	Mishell 01	Hemorrhage, weak, nausea, pale, cold, IV fluids administered	Hypotension	Hypotension
	076/199500069RU (Hispanic/American Indian, 19 yr old)	Haskell 02	Nausea, vomiting, cramping, hemorrhage and chlamydial infection.	Chlamydia infection	Urogenital disorder
	033/199500070RU (same as 199500444RU, added dizziness and headache, Caucasian, 52 days amenorrhea, 23 yr old)	Poppema 03	Hemorrhage requiring emergency suction, methergine administered. Syncope and pallor.	Heavy bleeding requiring aspiration Syncopal episode	Metrorrhagia Syncope Dizziness Headache
114 - 01/23/95	022/199500441RU (same as 199500064RU, added heavy bleeding requiring curettage (metrorrhagia), Caucasian, 56 days amenorrhea, 25 yr old)	Nichols 25	Severe cramping, feeling faint, hemorrhage, D&C and IV fluids required (hospitalized)	Increased cramping Hypotension/ hydration	Abdominal pain Hypotension Metrorrhagia
	050/199500065RU (Caucasian, 30 days amenorrhea, 30 yr old)	Poppema 03	Hemorrhage requiring D&C, dizziness, severe postural hypotension (hospitalized)	Heavy bleeding requiring curettage Severe postural hypotension	Metrorrhagia Postural hypotension
115 - 02/07/95	009/199500077RU (Caucasian, 57 days amenorrhea, 20 yr old)	Sheehan 26	Severe cramping, hemorrhage requiring D&C and hydration (IV fluids), dizziness and syncope (hospitalized)	Heavy bleeding/ curettage -IV hydration	Metrorrhagia

Protocol 166A/B - IND Safety Reports Submitted to the FDA

IND Submission (Number-Date)	Patient Identification/ International Drug Surveillance Number	Investigator and Clinic Number	Adverse Events Reported to FDA	Adverse Events as Reported by Roussel	Adverse Events as Coded by Roussel
118 - 02/15/95	062/199500102RU (Hispanic, 57 days amenorrhea, 28 yr old)	Mishell 01	Cramping, Hemorrhage requiring D&C (hospitalized)	Severe bleeding	Metrorrhagia
	107/199500443RU (Caucasian, 29 yr old)	Mishell 01	Weakness, dizziness, nausea and vomiting, IV fluids administered	Vomiting	Vomiting
				Severe nausea	Nausea
				Dizziness	Dizziness
	114/199500104RU (Hispanic, 62 days amenorrhea, 24 yr old)	Mishell 01	Hemorrhage, aspiration performed, methergine administered (hospitalized)	Severe bleeding	Metrorrhagia
	123 (Hispanic, 53 days amenorrhea, 23 yr old)	Mishell 01	Headache, dizziness, hemorrhage, IV fluids and methergine administered		
	037/199500106RU (Caucasian, 65 days amenorrhea, 29 yr old)	Tyson 04	Severe cramping, hemorrhage, D&C and IV fluids administered	Severe bleeding/ curettage-IV hydration	Metrorrhagia
119 - 02/17/95	109/199500100RU (Hispanic, 45 days amenorrhea, 22 yr old)	Mishell 01	Hemorrhage, D&C and IV fluids (hospitalized)	Severe bleeding	Metrorrhagia
	(follow-up)		Fever and IV antibiotics	Fever	Fever
	116/199500101RU (Caucasian, 33 yr old)	Mishell 01	Severe chest pain, EKG normal (hospitalized).	Severe chest pain	Chest pain
120 - 03/03/95	040/199500140RU (Caucasian, 51 days amenorrhea, 25 yr old)	Poppema 03	Hemorrhage, D&C, tachycardia (hospitalized)	Heavy menses/curettage no transfusion	Metrorrhagia
121 - 03/06/95	076 (African-American, 25 yr old)	Poppema 03	Cramping and hemorrhage, tx with methergine		
122 - 03/10/95	060/199500139RU (Caucasian, 54 days amenorrhea, 25 yr old)	Westhoff 24	Hemorrhage, hypotension, tachycardia, required IV fluids and 1 unit RBC	Heavy bleeding/ aspiration + transfusion	Metrorrhagia
				Hypotension	Hypotension

Protocol 166A/B - IND Safety Reports Submitted to the FDA

IND Submission (Number-Date)	Patient Identification/ International Drug Surveillance Number	Investigator and Clinic Number	Adverse Events Reported to FDA	Adverse Events as Reported by Roussel	Adverse Events as Coded by Roussel
123 - 03/13/95	017/199500135RU (Caucasian, 57 days amenorrhea, 24 yr old)	[redacted]	Hemorrhage, orthostatic hypotension, given IV fluids, oxytocin, D&C	Bleeding/ curettage orthostatic hypotension	Metrorrhagia Postural hypotension
	070 (Caucasian, 28 yr old)	Haskell 02	Gunshot (hospitalized)		
124 - 04/11/95	030/199500175RU (Caucasian, 52 days amenorrhea, 36 yr old)	[redacted]	Hemorrhage, syncope, hypotension, tachycardia, required IV fluids and surgical procedure	Bleeding/ surgical procedure/IV fluids, syncope	Metrorrhagia Syncope
	032/199500446RU (Caucasian, 27 yr old)	[redacted]	Vasovagal reaction required IV fluids	Vasovagal reaction/IV fluids/ antihistamines	Syncope
	035/199500447RU (East Asian, 20 yr old)	[redacted]	Hemorrhage required IV fluids and oxytocin	Heavy bleeding	Metrorrhagia
	037/199500176RU (African, 51 days amenorrhea, 26 yr old)	[redacted]	Dizziness, shortness of breath, hemorrhage required D&C, IV fluids and oxytocin	Heavy bleeding requiring aspiration	Metrorrhagia
	081/199500172RU (Caucasian, 51 days amenorrhea, 28 yr old)	Sheehan 26	Hemorrhage, syncope leading to injury of neck (hospitalized, surgical abortion not reported in Med Watch)	Heavy bleeding/surgical abortion Faint leading to neck injury	Metrorrhagia Syncope
125 - 04/19/95	158/199500179RU (Caucasian, 54 days amenorrhea, 24 yr old)	Haskell 02	Hemorrhage, D&C weakness, fatigue required IV fluids and methergine	Excessive bleeding curettage + IV fluids	Metrorrhagia
	159 (Hispanic, 50 days amenorrhea, 35 yr old)	Mishell 01	Hemorrhage/IV fluids and methergine (surgical rescue, not in Med Watch)		

Protocol 166A/B - IND Safety Reports Submitted to the FDA

IND Submission (Number-Date)	Patient Identification/ International Drug Surveillance Number	Investigator and Clinic Number	Adverse Events Reported to FDA	Adverse Events as Reported by Roussel	Adverse Events as Coded by Roussel
132 - 06/07/95	036/199500247RU (Caucasian, 23 yr old)	Dean 27	Pneumonia unrelated to study drugs (hospitalized)	Severe pneumonia	Pneumonia
	012/199500248RU (Caucasian, 53 days amenorrhea, 31 yr old)	Sogor 29	Hemorrhage, cramping, weakness, faintness required D&C (hospitalized)	Heavy bleeding-D&C	Metrorrhagia
	028/199500249RU (Caucasian, 26 yr old)	Tyson 04	Hemorrhage, dizziness, weakness, Methergine administered. Conceived two days after mifepristone	Bleeding-pregnancy post abortion by 38486	Metrorrhagia
	075/199500448RU (Caucasian, 24 yr old)	Tyson 04	Nausea, dizziness required IV fluids	Dehydration	Dehydration
	004/199500251RU (African-American, 55 days amenorrhea, 25 yr old)	Creinin 28	Hemorrhage, aspiration. IV for access only, methergine administered (hospitalized)	Heavy bleeding/surgical aspiration	Metrorrhagia
133 - 06/13/95	027/199500455RU (Caucasian, 50 days amenorrhea, 25 yr old)	Creinin 28	Vomiting, hemorrhage, D&C lightheadedness required IV fluids (hospitalized)	Bleeding/ curettage/IV fluids	Metrorrhagia
136 - 07/18/95	071/199500329RU (same as 199500449RU, added IV fluids, African-American, 55 days amenorrhea, 27 yr old)		Vomiting, hemorrhage, dizziness required D&C and IV fluids (hospitalized)	Vomiting after misoprostol, heavy bleeding/D&C, dizziness	Vomiting Metrorrhagia Dizziness
	030/199500330RU (African-American, 19 yr old)	Creinin 28	Hemorrhage	Bleeding/No action taken	Metrorrhagia
138 - 07/25/95	033/199500454RU (African-American, 46 days amenorrhea, 21 yr old)	Creinin 28	Hemorrhage required D&C, patient lost to follow-up (hospitalized)	Heavy bleeding/D&C	Metrorrhagia
139 - 07/28/95	063/199500340RU (Caucasian, 50 days amenorrhea, 30 yr old)	Creinin 28	Anxiety attack, alcohol withdrawal, threatened suicide, severe depression (hospitalized)	Threatened suicide	Depression

Protocol 166A/B - IND Safety Reports Submitted to the FDA

IND Submission (Number-Date)	Patient Identification/ International Drug Surveillance Number	Investigator and Clinic Number	Adverse Events Reported to FDA	Adverse Events as Reported by Roussel	Adverse Events as Coded by Roussel
141 - 08/04/95	147/199500342RU (Caucasian, 21 yr old)	Dean 27	Viral meningitis (hospitalized)	Viral meningitis	Meningitis
143 - 08/09/95	074/199500450RU (same as 199500355RU, added anemia 9.2 g/dl, Caucasian, 60 days amenorrhea, 31 yr old)	Creinin 28	Hemorrhage and passed out, required aspiration and IV fluids and methergine (hospitalized)	Gushing of blood/aspiration/ IV fluids Hypotension	Metrorrhagia Hypotension Anemia
	088/199500356RU (Caucasian, 62 days amenorrhea, 20 yr old)	Creinin 28	Hemorrhage required IV access, methergine administered	Heavy bleeding/suction-curettage	Metrorrhagia
144 - 08/10/95 (follow-up)	088/199500451RU (same as 199500356RU)	Creinin 28	Hemorrhage, suction curettage performed, methergine (hospitalized)	Heavy bleeding/ methergine	Metrorrhagia
145 - 08/15/95	018/199500365RU (African-American, 42 days amenorrhea, 29 yr old) 019/199500366RU (Caucasian, 28 yr old)	Malloy 07 Malloy 07	Abdominal pain due to retained tissue, required uterine aspiration Hemorrhage	Abdominal pain incomplete abortion Heavy bleeding	Abdominal pain Metrorrhagia
146 - 08/25/95	104/199500452RU (Caucasian, 62 days amenorrhea, 39 yr old)	Creinin 28	Hemorrhage, severe cramping required D&C, IV fluids and methergine (hospitalized)	Heavy bleeding Severe cramps	Metrorrhagia Uterine spasm
147 - 09/01/95	108/199500375RU (two forms - one patient, Caucasian, 63 days amenorrhea, 21 yr old)	Creinin 28 Creinin 28	Severe cramping Fever, tender uterus required D&C and aspiration. Methergine administered (hospitalized).	Severe cramping (incomplete abortion) Fever (antibiotics + curettage)	Abdominal pain Fever
149 - 09/21/95	116/199500453RU (African-American, 61 days amenorrhea, 27 yr old)	Westhoff 24	Cramps, heavy bleeding, fever, endometritis, required IV fluids and vacuum aspiration	Heavy bleeding/IV fluids Endometritis/ antibiotics	Metrorrhagia Endometrial disorder
154 - 11/02/95	165/199500427RU (Caucasian, 60 days amenorrhea, 20 yr old)	Nichols 25	Excessive bleeding, dizziness required D&C and IV fluids (hospitalized)	Excessive bleeding D&C Dizziness/ IV fluids	Metrorrhagia Malaise

The Population Council

Center for
omedical Research

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October 2, 1995

RECD
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HFD-510

Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research
Document Control Room 14B-03
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
CSO INITIALS DATE

Subject: IND —— Mifepristone Tablets, 200 mg
Submission Serial Number: 151
Pre-NDA Meeting between the
Population Council and FDA Staff
Regarding the NDA on Mifepristone

Dear —

Attached please find 20 copies of:

1. The suggested agenda for the meeting.

2. An outline of the topics to be discussed at the meeting.

The individuals that will attend the meeting from the Population Council will be:

C. Wayne Bardin

W. G. Coln

Ann Robbins

Should you need additional information, do not hesitate to contact me. Best regards.

Sincerely yours,

C W Bardin

C. Wayne Bardin

CWB:yah
cc: W. G. Coln
A. Robbins

PRE-NDA MEETING ON MIFEPRISTONE BETWEEN THE POPULATION COUNCIL AND THE FDA

Attending for The Population Council:

Dr. C. Wayne Bardin
Dr. Ann Robbins
Mr. W.G. Coln

Proposed Agenda

1. **Brief History of Project**
2. **Status of US Clinical Trials**
3. **Status of New Manufacturers of Drug Substance and Drug Product**
4. **Organization and Content of NDA**
5. **Audit of French Clinics**
6. **Strategy and Timing of Submission of Additional Information to NDA**

IND ——

Mifepristone Tablets, 200 mg

OUTLINE OF INFORMATION ON MIFEPRISTONE TO BE DISCUSSED AT THE PRE-NDA MEETING BETWEEN THE POPULATION COUNCIL AND THE FDA

The Population Council
New York, NY 10021

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2.	Status of US Clinical Trials	2
3.	Status of New Manufacturers of Drug Substance and Drug Product	3
4.	Organization and Content of NDA	4
5.	Audit of French Clinics	7
6.	Strategy and Timing of Submission of Additional Information to NDA	8

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1. Brief History of Project

1983	Population Council files INDs and begins clinical program	
	IND	Mifepristone in Induction of Abortion
	IND	[redacted]
1993 - 1994	Population Council initiates efforts toward development of NDA for use in the induction of abortion and meets with FDA regarding planning and contents of submission	
1994	Population Council is granted ownership of product in US	
1994	Population Council initiates two major clinical trials in US	
1995	Population Council anticipates submission of NDA by year end	

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2. Status of US Clinical Trials

Total Number of Subjects Enrolled = 2,115

Enrollment Completed on September 1, 1995

Number of Case Record Forms Currently Entered into Database = 50%

US Clinical Studies A and B
Enrollment and Results by Amenorrhea Group
(As of September 10, 1995)

Amenorrhea Group	Total Number of Subjects Enrolled	Total Number of Abortions	Total Number of Complete Medical Abortions	Success Rate (Complete Medical Abortions as Percent of Total Abortions)
Group I ≤ 49 Days	849	833	775	93.04
Group 2 50-56 Days	726	693	599	86.44
Group 3 57-63 Days	540	515	422	81.94
Total	2115	2041	1796	88.00

3. Status of New Manufacturers of Drug Substance and Drug Product

a. Manufacturer of Drug Substance

i. Contract has been concluded.

ii. New synthesis development is well advanced.

b. Manufacturer of Drug Product

i. Manufacturer has been identified.

ii. Conclusion of contract is imminent.

4. Organization and Content of NDA

a. **Following NDA Sections Are Being Prepared in Accordance with FDA Guidelines**

Item 1. **Index**

Item 2. **Summary**

Item 5. **Nonclinical Pharmacology/Toxicology**

All included studies were previously submitted to IND

Submission has a cut-off date of August 1, 1995 and several studies have been received from Roussel Uclaf since that time. These studies have been submitted to the IND and will be included in the NDA Safety Update.

Item 6. **Human Pharmacokinetics/Bioavailability**

All included studies were previously submitted to IND

4. Organization and Content of NDA (Cont.)

b. Following NDA Sections Have Unique Features

Item 3. Chemistry, Manufacturing and Controls

Initial NDA submission will name Roussel Uclaf as the manufacturer of drug substance and drug product. To preserve confidentiality, Roussel will submit the complete CMC section directly to IND —— The Population Council will not have access to this information and can include only a letter of authorization/cross-reference to the Roussel submission in this section of the NDA.

Supplement(s) will be submitted to the NDA to provide for new manufacturers.

Field Copy (NY District)

For CMC information component, field copy will include only the letter of authorization/cross-reference to the Roussel submission.

Item 4. Samples, Methods Validation and Labeling

The Population Council does not have access to Roussel methods validation information for this section. Roussel will prepare four copies of the section for submission to FDA.

Samples will be submitted to FDA by Roussel directly or via The Population Council.

4. Organization and Content of NDA (Cont.)

b. Following NDA Sections Have Unique Features (Cont.)

Item 8. Clinical

Initial NDA submission will request approval for use in induction of abortion in patients with amenorrhea of ≤ 49 days.

All studies are regarded as historically controlled.

Pivotal studies in the submission are the two primary French studies (FFR/91/486/14 and FF/92/486/24).

Integrated Summary of Efficacy will discuss only the two pivotal French studies.

Integrated Summary of Safety will discuss experience in all studies.

Submission will include an interim safety report on the two US clinical studies now being completed.

Submission has a cut-off date of August 1, 1995 and several studies have been received from Roussel Uclaf since that time. These studies are being submitted to the IND and will be included in the NDA Safety Update.

Item 11. Case Report Form Tabulations
Item 12. Case Report Forms

Case report form tabulations and case report forms will be submitted only for patients in the two pivotal French studies.