WEEKLY REPORT -- (July 29 - August 16, 1996)

AGENCY/OFFICE: FDA

Advisory Panel Recommends RU-486. On July 19, in a meeting that attracted extensive media attention, an FDA advisory panel concluded 6 to 0 (with two abstentions) that the benefits of mifepristone (RU-486) outweigh its risks for the interruption of early pregnancy. The Population Council, a non-profit research organization and sponsor of the RU-486 application, presented data from two French trials in 2, 480 women that showed the combination of RU-486 and an oral prostaglandin to be about 95 percent effective. Safety data from U.S. trials in more than 2000 women were also presented to compare how the U.S. experience relates to the European data. . Approximately 35 individuals made comments during the open public hearing portion of the meeting. The panel recommended post-marketing studies to gather further information about the actual application of this regimen in the U.S.

WEEKLY REPORT – (July 22 - August 9, 1996)

AGENCY/OFFICE: FDA

Advisory Committee Meeting to Review RU-486. An FDA advisory panel will meet on July 19 to discuss the new drug application (NDA) for mifepristone (RU-486) for the interruption of early pregnancy. A number of anti-abortion groups wrote Commissioner Kessler a letter on July 10, asking for the cancellation of the advisory committee meeting. The letter alleges that as many as five of the advisory committee members may have a direct or apparent conflict of interest because of a financial interest in organizations that provide abortions or because of other biases. FDA responded to the letter on July 16, assuring the groups that the Agency consulted with the HHS Office of the Special Counsel for Ethics and the U.S. Office of Government Ethics, who found no violations of any ethics law or regulations (thereby obviating the need to consider cancellation of the meeting). On a related note, recent consumer letters to FDA supporting approval of RU-486 ——— outnumber those against approval.

WEEKLY REPORT -- (MARCH 13 - MARCH 31, 1995)

AGENCY/OFFICE: FDA

Citizen Petition on RU-486: On February 28, Americans United for Life, members of Congress (including Thomas J. Bliley, Jr.), and others submitted a citizen petition to FDA specifically requesting that the Commissioner refuse to approve any NDA for RU-486 for use as a pharmaceutical abortifacient. The petitioners are concerned, in part, that RU-486 could be approved in the U.S. based largely on foreign data, with only limited safety data generated from studies conducted in the U.S.

WEEKLY REPORT -- (May 16-22, 1994)

AGENCY/OFFICE: FDA **DATE:** May 10, 1994

CONGRESSIONAL ACTIVITIES

Subject: RU-486
Date: May 16

The House of Representatives Subcommittee on Regulation, Business Opportunities and Technology has scheduled a hearing to discuss various issued related to the abortifacient drug RU 486.

WEEKLY REPORT -- (May 23-27, 1994)

AGENCY/OFFICE: FDA **DATE:** May 18, 1994

CONGRESSIONAL ACTIVITIES

Subject: RU-486
Date: May 16

After months of complex negotiations, Secretary Shalala announced at a press conference, in Washington, D.C., that the French pharmaceutical company Roussel Uclaf, at the encouragement of the Clinton Administration, is donating its United States patent rights for RU-486 to the Population Council, Inc., a not-for-profit corporation. FDA plans to do all it can to quickly evaluate RU-486 once the Population Council conducts clinical trials, identifies a manufacturer and submits a new drug application to the FDA.

6. Mifepristone Petition - On March 20, 1995, a letter was sent to Mr. Gary Yingling, responding to his February 28, 1995, petition regarding FDA review of an NDA for mifepristone as an abortifacient. The letter notes that the petition has stated many concerns and considerations related to the safe and effective use of mifepristone for this indication. It notes that FDA is prohibited from publicly disclosing the existence of an application, however, if, and when, such an application is submitted to the Agency, it will be reviewed in accordance with the statutory criteria set forth in the FD&C Act. Such a review requires the Agency to review both the safety and effectiveness of the drug, among other factors. (Contact: ———

OFFICE OF THE COMMISSIONER MEETING
EXECUTIVE SUMMARY

Date: July 14, 2000
Time: 11:30 – 12:00 PM
Location: Rm. 14-68, PKLN

Subject: Mifepristone

Attendees: Jane Henney, [redacted]

Meeting Purpose: To provide an update on the review of mifepristone.

Meeting Agenda: [redacted] will lead the briefing.

Background: Mifepristone, also know as RU 486, is an abortifacient to be used with misoprostol for medical abortion. Mifepristone is being reviewed by CDER with a PDUFA date of September 30, 2000. The drug's sponsor, The Population Council (PC), has three areas to address from the last approvable action of February 18, 2000: chemistry/manufacturing, distribution system, and labeling.

Chemistry/manufacturing - In May 2000, FDA was informed that the manufacturing processes for the drug substance have been changed from how the NDA described the process. These changes are significant and require pre- and post-change comparative physical, analytical, and stability data to demonstrate that quality is maintained. The sponsor is responsible for supplying physical and analytical data by mid-July and stability data sometime in September. [redacted] The inspection of the Chinese drug substance maker is scheduled for July 27 and 28.

Distribution System - On July 5, 2000, the sponsor proposed that mifepristone be directly distributed to health care providers who self-attest to specific qualifications. PC proposes that the drug be provided by or under the supervision of a physician who has the ability to assess the duration of pregnancy accurately, to diagnose ectopic pregnancies, and to assure patient access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions and emergency resuscitation. The sponsor does not believe it is necessary for prescribers to possess all the qualifications needed to perform every step in the patient's care. PC believes the prescriber can be advised to plan for care such as handling of incomplete abortions and the need for surgery and to give patient information about how to obtain these types of care. The sponsor does not propose health care providers who are distributing this drug be trained in the use of this drug, but the sponsor is making available educational programs. The sponsor also objects to approving this drug under Subpart H's provision for restricted distribution [redacted]

Labeling - The sponsor

Executive Secretariat Contact:

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF THE COMMISSIONER MEETING
EXECUTIVE SUMMARY

Date: August 11, 2000
Time: 11:00 a.m. – 12:00 noon
Location: Rm. 14-68, PKLN

Subject: Mifepristone

Attendees: Jane Henney, [redacted]

Meeting Purpose: To provide an update on the review of mifepristone.

Meeting Agenda: [redacted] will lead the briefing.

Background: [redacted] talking points are attached.

Executive Secretariat Contact: [redacted]

APPEARS THIS WAY
ON ORIGINAL

Mifepristone Outstanding Issues 8-11-00

- Chemistry and Manufacturing
  - 483 issued 7/28/00 with minor deficiencies to be corrected by 8/30/00
  - Analytic and stability data outstanding

- Labeling
  - Black Box
    - Surgical intervention may be necessary; prescribers should determine in advance whether they will provide such care or refer. Patients should be given clear instructions on whom to call and what to do. Patients should receive Med Guide, read and discuss it and Patient Agreement
  - Day 3 return for misoprostol
    - FDA: Return on Day 3 for misoprostol;

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Distribution System: Physician Qualifications
  - [redacted] distribution of drug to physicians who do not possess surgical intervention skills, but must be able to date pregnancies, diagnose ectopics, and assure referral to physician with surgical skills, if needed.
  - For safety reasons, we need to ensure quality of outcomes [redacted] those patients treated by physicians who possess surgical intervention skills (as in the clinical trials) and by physicians who refer patients for surgical intervention.
    - Four of six Phase 4 commitments become part of risk management/monitoring system to ensure quality:
      - To monitor the adequacy of distribution system and credentialing
      - To follow up on medical failure outcomes [redacted]
      - To ascertain completion of regimen
      - To study outcomes of children born after treatment failure
        - » Audit patient agreement? 2% chart audit versus confidentiality issues
        - » Study of referral/non-referral practices on rates of med failure, return rates for day 14, transfusion, hospitalization, surgical intervention for bleeding, infection rates
        - » Return rates for day 14 collected above. Consider nested case-control study with data collection on patient variables who don't return versus who do.
        - » Study of a sample of above practices supplemented with spontaneous reports on pregnancy outcomes of infants exposed

Mifepristone Outstanding Issues 8-11-00/ cont.'

- Remaining Phase 4 Studies
  - Two other studies : [redacted]
    - Assess long term effects in multiple use (European data)
    - Assess S/E in women under age 18, over 35, and in smokers

- Medication Guide

  [redacted]

  - [redacted]
  - Ensure distribution of Guide through unit of use packaging, attestation of distribution by physician when signing to receive drug

- Subpart H
  - Pop Council requests language [redacted]

From:
Sent: Thursday, August 10, 2000 8:21 AM
To: (OC)
Subject: mifepristone

Sensitivity: Confidential

Drafts for 8/11 briefing

APPEARS THIS WAY
ON ORIGINAL

From: [redacted] on behalf of [redacted]
Sent: Monday, October 16, 2000 10:23 AM
To: [redacted]
Subject: FW: Coorespondance Regarding Mifepristone

---Original Message---
From: [redacted]
Sent: Sunday, October 15, 2000 5:28 PM
To: ORA Public Affairs Specialists; ORA Public Affairs Liaisons
Cc: ORA DDs; ORA RFDDs; [redacted]
Subject: Coorespondance Regarding Mifepristone

Several individuals have asked how the agency is handling written correspondence (emails, letters, etc.) on Mifeprestone (RU-486). If you receive any correspondence in the field, please forward it to the Center for Drug Evaluation and Research (CDER) OTCOM, Division of Drug Information, HFD-210, 5600 Fishers Lane, Rockville, MD 20857. CDER's office will coordinate all responses for the agency.

Further, if you receive emails, please forward them to druginfo@cder.fda.gov.

Again, any media inquires should be referred to OPA. Thanks! [redacted]

[redacted]

Office of Public Affairs, HFI-3
phone: [redacted]
fax: [redacted]

APPEARS THIS WAY
ON ORIGINAL

EXECSEC

From: Henney, Jane
Sent: Wednesday, September 27, 2000 1:35 PM
To: EXECSEC
Subject: FW: Script folks may use re: RU 486 telephone calls

From:
Sent: Wednesday, September 27, 2000 1:34:42 PM
To:
Cc:
; Henney, Jane;
Subject: Script folks may use re: RU 486 telephone calls
Auto forwarded by a Rule

This is a script FDA staff, e.g., in the OC and in the office may use when answering phone calls re: RU 486.

A: Office of the Commissioner

Caller: What is your name...who are you?

A: (You may give your office name and you may withhold your name, if you'd like.)

Caller: I'm calling about (mifepristone, mifeprex, misoprostle, RU 486, the Population (POP) Council drug approval, the abortion pill, etc.)

A: Hold on while I transfer you to the FDA people who are answering these calls...if you accidentally get cut off, I'm transferring you to 301-827-4570 (or you may transfer the call to 888-infoFDA) - . (If they identify themselves as congressional staff, transfer them to 301-827-0087 or if they are other gov't officials, transfer them to FDA exec sec at 301-827-4450.)

Caller: I don't want to be transferred (or I've already been transferred and the line is busy)...I want to talk with you or someone at this number.

A: I'm sorry, but all calls on this subject are being handled by one group of people. I'll be happy to take your name and number and forward it to the appropriate office. Or, you may write to the agency. (see addresses below.)

Caller: Who can I write to?

A: email: druginfo@cder.fda.gov

address: FDA
5600 Fishers Lane
OTCOM/CDER, HFD-200
Rockville, Md. 20857

fax: 301-827-4577

Caller: Is this the Commissioner's office?

A: This is the Office of the Commissioner

Caller: I would like to leave a message for the Commissioner on this subject.

A: Sure, let me transfer you to a phone where you can leave a message (and then transfer to OTCOM - the 827 or 888 number above.)

Caller: How can I get more information on this topic?

A: The internet site is: http://www.fda.gov/cder/drug/infopage/mifepristone

Caller: (begins to cuss, say inappropriate things)

A: I'm sorry but I'm going to have to end this conversation.

Caller: (threatens the building, people, or the Commissioner)

A: (refer to security email/security procedures)

Caller: What do you think about the abortion pill...what is your opinion on FDA's action.

A: I'm sorry, but it is not appropriate for me to answer that question. If you'd like to comment or ask questions, call 301-827-4570 or 888-infofda (or refer them to the internet site.)

EXECSEC

From: EXECSEC
Sent: Friday, September 29, 2000 3:37 PM
To:
Subject: FW: Request

—Original Message—
From: EXECSEC
Sent: Friday, September 29, 2000 3:37 PM
To:
Subject: Request

Office Heads:

Please forward the attached note to appropriate staffers that worked on the rollout.

Exec. Sec.

kudos.doc

APPEARS THIS WAY
ON ORIGINAL

Dear Colleagues,

I would like to personally thank each of you for your efforts in planning and conducting all aspects of the roll-out for the mifepristone approval. This team effort was critical in ensuring that the approval decision was communicated in a clear and timely manner to all interested parties. The conference calls with health professional and women's groups, the press interviews, the preparation of information for our Web site, and the calls, faxes, and e-mails to various other constituents resulted in delivery of a coordinated and coherent message regarding the approval. I appreciate the extra hours that some of you worked to make this happen. With an approval of this nature, which has engendered wide-ranging attention and equally wide-ranging reaction, I am grateful that together we have communicated the role of the FDA in a simple and forthright manner.

Jane E. Henney, M.D.
Commissioner of Food & Drugs

APPEARS THIS WAY
ON ORIGINAL

EXECSEC

From: EXECSEC
Sent: Fridav. October 06, 2000 7:22 AM
To:
Subject: FW: Proposed Legislation on Mifepristone

Please bring to Dr. Henney's attention.

Exec. Sec.

----Original Message----
From: Henney, Jane
Sent: Thursday, October 05, 2000 5:57 PM
To: EXECSEC
Subject: FW: Proposed Legislation on Mifepristone

From:
Sent: Thursday, October 05, 2000 5:56:44 PM
To: Henney, Jane;
Cc:
Subject: RE: Proposed Legislation on Mifepristone
Auto forwarded by a Rule

FYI

Rep. Coburn did introduce the attached legislation on October 4 as HR 5385. He had 43 co-sponosrs

FDA/OL/OPPL

fax -

----Original Message----
From:
Sent: Wednesday, October 04, 2000 7:07 PM
To: Henney, Jane;
Cc:
Subject: Proposed Legislation on Mifepristone
Importance: High

Please find attached what we believe to be the legislation proposed by Rep. Coburn on limiting access to mifepristone. We have been told this is the proposal, however, we are not certain it has been filed yet and will not know until Thursday. Also below is language said to have been circulated by Rep. Coburn's office in suport of the legislation. If these versions change we will circulate new versions as soon as available.

<< File: coburn_095.pdf >>

> "COBURN OFFICE Summary of
> RU-486 Patient Health and Safety Protection Act
>
> The purpose of this bill is to protect mothers from the irresponsible and
> politically motivated malpractice of the Food and Drug Administration in
> approving this drug without safeguards. It is to ensure that RU-486 kills
> only one person at a time instead of two at a time.
>
> This bill simply codifies the patient protection standards that were
> reportedly considered by the FDA prior to approval of RU-486, but which
> were evidently dropped under political pressure from the abortion lobby.

>
> 1) The prescribing physician must be qualified to handle
> complication of an incomplete abortion. Basically, the prescribing
> physician must be able to do a dilation and curettage (d & c) in the event
> of an incomplete abortion. According to the clinical trials in the US,
> approximately 5% of the women who used this method of abortion prior to
> seven weeks LMP experienced an incomplete abortion. (Among the entire
> clinical trial population, which included those who had been pregnant
> longer, it was about 15%.) An incomplete abortion left untreated is a
> very serious, potentially fatal, complication.
>
> 2) The prescribing physician must be legally empowered to commit an
> abortion and trained to do so. The training standard is essentially the
> same as point 1; the legal standard is just current law.
>
> 3) The prescribing physician must be qualified to read a sonogram in
> order to date the pregnancy and identify an ectopic pregnancy. The
> effectiveness of RU-486 in killing the baby is sharply reduced after seven
> weeks, while the rate of complications is much higher. The use of RU-486
> in the case of an ectopic pregnancy is not recommended at all for the sake
> of the mother.
>
> 4) The prescribing physician must be properly trained in the
> administration of this drug. Doctors who don't know what they are doing
> are likely to hurt their patients.
>
> 5) The physician must have admitting privileges at a nearby
> hospital. Complications requiring emergency care, such as heavy bleeding,
> are relatively common with the use of this drug combination, and the
> prescribing physician must take responsibility for the care of his/her
> patients. If complications do arise, and the attending doctor is out of
> range or unavailable to care for his/her patient, other doctors who may
> have moral and ethical objections to abortion are then put in a position
> of having to perform the surgical abortion.
>
> The Coburn bill simply enacts these provision into law except for the
> provision creating a national registry of RU-486 providers and the
> provision calling for a follow-up study. Coburn believes these provisions
> should be left to the discretion of the Secretary of the Department of
> Health and Human Services."

Thanks

[redacted]

FDA/OL/OPPL

[redacted]

fax - [redacted]

[redacted]

APPEARS THIS WAY
ON ORIGINAL

[redacted]

.....
(Original Signature of Member)

106TH CONGRESS
2D SESSION

H. R. _____

IN THE HOUSE OF REPRESENTATIVES

Mr. COBURN introduced the following bill; which was referred to the Committee on _____

A BILL

To require the Food and Drug Administration to establish restrictions regarding the qualifications of physicians to prescribe the abortion drug commonly known as RU-486.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

October 3, 2000

SECTION 1. SHORT TITLE.

This Act may be cited as the "RU-486 Patient Health and Safety Protection Act".

SEC. 2. ESTABLISHMENT OF RESTRICTIONS REGARDING PRESCRIBING OF CERTAIN ABORTION DRUG.

With respect to the application that was submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the drug mifepristone (commonly referred to as RU-486, to be marketed as MIFEPREX), and that was approved on September 28, 2000, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall promptly modify the conditions of the approval of such drug to establish the additional restriction that the drug may not be prescribed by any person other than a licensed physician who meets the following requirements:

(1) The physician is qualified to handle complications resulting from an incomplete abortion or ectopic pregnancy.

(2) The physician has been trained to perform surgical abortions and has met all applicable legal requirements to perform such abortions.

(3) The physician is certified for ultrasound dating of pregnancy and detecting ectopic pregnancy.

(4) The physician has completed a program regarding the prescribing of such drug that uses a curriculum approved by the Secretary.

(5) The physician has admitting privileges at a hospital to which the physician can travel in one hour or less, determined on the basis of starting at the principal medical office of the physician and traveling to the hospital, using the transportation means normally used by the physician to travel to the hospital, and under the average conditions of travel for the physician.

... ASSIGNED: 7 / 96 | PRIORITY: 2 | DATE INSP 7-1/5-96 | GRP
CENTRAL FILE NO | JD/TA: | CNTY | PHONE
EMPL NO ____

NAME: Dr. H. Quiquempois | STREET Centre Hospitalier, d'Orthogenie

CITY: 59322 Valenciennes | STATE France | ZIP: | DISTRICT

ENDORSEMENT

The Population Council, New York has filed NDA-20687, Roussel's abortion pill RU-486 (________) which relies in part on studies conducted by Dr. Quiquempois' predecessor Dr. Claudine Van Geem.

Both studies FFR/91/486/14 and 24 were covered, following which FD-483 was issued. There was a failure to follow protocol exclusion requirements, such as patients who were heavy smokers, overage subjects, or patients past the 63-day amenorrhea limit, or combinations thereof. Records were not complete, with laboratory or ultrasound records missing. Theee was also a failure to notify the sponsor Roussel within 24 hours of a serious adverse event, and did not do so for about two months.

Classified VAI

APPEARS THIS WAY
ON ORIGINAL

VOLUNTARY CORRECTION DATA

PAC	PROBLEM TYPE	CORRECTIVE ACTION	EST COST OF ACTION	DATE ACTION VERIFIED	CORRECTING UNIT	REPORTING DISTRICT

SIGNATURE /S/ | DATE 11/12/[illegible]

Supervisory Investigator

DISTRIBUTION:

DAL-DO - O W/O Exhibits
HFD-344 - cc w/O Exhibits
HFC-133 - cc w/out Exhibits
FS - CHRONO, ICAN, & [illegible] tor 1483
[illegible] - cc W/O Exhibits

FORM FDA 481(E)-CC (10/81)

MIF 004024

ASSIGNED 7/96 PRIORITY 2 DATE INSP. 7-1/5-96 GRP

ENTERED FILE NO. SD/TA CNTY PHONE

NAME Dr. H. Quiquempois STREET Centre Hospitalier, d'Orthogenie

CITY 59322 Valenciennes STATE France ZIP DISTRICT:

RELATED FIRMS none ST-ASSGN ITS.

REGISTRATION

REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR
	/	/	/		/	/	/		/	/	/
	/	/	/		/	/	/		/	/	/

ESTABLISHMENT TYPES/ 1. 2. 3.
INDUSTRY CODES ON OEI.

TOTAL ESTAB. SIZE	U.S. BUSINESS RECEIVED	SOLD	DISTRICT USE #1	#2	#3	RECALL NO.	REFUSAL CODE	PROFIL	PASS FAIL
1	YES NO	Ø				Ø	Ø		

ESTAB-CHANGES NEW-FIRM NONE NAME ADDRESS OWNERSHIP SIZE PROD CODE
OTHER: EST-TYPE O/B INACTIVE NOT OEI AUA-FIRM REGISTRATION

PAC	PROCESS (PRODUCT) CODE	EST TYPE	INSP BASIS	EMPL1 PC NO HD	EMPL2 PC NO HD	EMPL3 PC NO HD	PRODUCT	PR IT Y	RESC HED DATE	INSP CONC	DIST DCSN
48R806	61Z	7	2	—			Protocols FFR/91/486/14 and 24		—	A	E

SAMPLES COLLECTED:
SAMPLE# Ø PRODUCT. Ø

HEADQUARTERS UNIT REFERRED HFC-134, HFD-344

FD 483 ISSUED YES NO

REASON REFERRED routine

OTHER FED GOVT INSP OR GRADING

INSPECTOR'S NAME/SIGNATURE

/S/ , HFD-344

SUPERVISOR'S NAME/SIGNATURE

/S/

FORM FDA 461(A)-CG (09/84)

PRODUCTS COVERED

EMPL NO.: 101

ESTABLISHMENT NAME: Dr. H. Quiquempois

DATE INSPECTED: 7-1/5-96

DATE ASSIGNED: 7 /96

DATE COVERED	PRODUCT CODE	TEST TYP	TEST TYP	TEST TYP	PRODUCT DESCRIPTION
7/ 1/96	61Z	7			Protocols FFR/91/486/14 and 24, Roussel's RU-486
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APPEARS THIS WAY
ON ORIGINAL

FORM FDA 461(C)-CG (10/80)

EIR
Dr. H. Quiquempois
Center Hospitalier de Valenciennes
Unite d'Orthogenie
Avenue Desandrouin B.P. 479
59322 Valenciennes, France

Investigators: [redacted]

SUMMARY OF FINDINGS

The Population Council, New York City, New York, has filed NDA 20-687 for Mifepristone to be used in conjunction with a prostiglandin as an abortion pill. The drug sponsor is Roussel, but there were no USA studies at that time, the only clinical studies having been conducted in France.

This firm conducted two studies, FFR/91/486/14 and FF/92/486/24. These were done starting in 1991 and 19992, respectively. Both studies were audited, and representative records from each of the studies were reviewed, which revealed a failure to follow protocol exclusion requirements; e.g., Study 24, at least 22 patients entered were smokers (exceeding the protocol smoking limits). Forty-eight patients were over age, some of which were also smokers, and four patients exceeded the 63-day amenorrhea limits. Some of these were also over age or smoking.

There was also a failure to maintain complete and accurate study records; e.g., for Study 14, 56 sets of patient files were checked, of which 25 had laboratory reports missing or the date reported was in error. Twenty-one of 56 sets of records had ultrasound records missing or the date reported was in error. For Study 24, of 92 subject records checked, 3 ultrasound records were missing or the date reported was in error.

There was also a failure to follow protocol requirements to notify the sponsor firm Roussel within 24-hours of the serious adverse event, such as did occur on April 23, 1993, when the firm finally notified Roussel of a patient's hospitalization and transfusion that had occurred on February 11, 1993.

Nevertheless, CDER's (HFD-344) [redacted] who accompanied on this inspection, assured the firm that he would not recommend that the study not be accepted.

PURPOSE OF INSPECTION

The Population Council of New York City has filed NDA 20-687 for Mifepristone as a pill to cause abortion, based on the work of manufacturer Roussel and their clinical studies in France beginning in 1991 and 1992. Since there were no corresponding clinical studies in the USA, this firm, along with clinical investigator Dr. Elisabeth Aubeny's firm in Paris, were two sites selected to be audited, based on their relatively large number of patients enrolled in studies FF-92/486/24 and FFR/91/486/14. Both studies were covered during the current inspection.

FIRM FACILITIES

This is an abortion clinic which is a part of Centre Hospitalier de Valencienns, Unite d'Orthogenie. Under French law, a woman who wants an abortion must have a referral from her physician to the physician who performs the abortion, so that two physician approvals are necessary. Therefore, for many of the records examined, there were documents from outside laboratories and outside physicians that were not part of this facility.

PERSONS INTERVIEWED

At the time these studies were conducted, the person in charge was [redacted] but she is no longer connected with this facility, and now works at [redacted]

[redacted] was not contacted during this inspection.

The person in charge now, who is the custodian of the records, is Dr. H. Quiquempois. All pertinent discussion was with him, and throughout the inspection, as had been the situation during the inspection of the related center in Paris, our translator was [redacted]

Co-investigators at the time of the study included [redacted] We did meet [redacted] just briefly on the 2nd of July, but Dr. Quiquempois ordered him excused for the duration of the inspection, because of ' according to [redacted] So although at the conclusion of the inspection, an FDA-483 Form was made out to Dr. Quiquempois, custodian of records, and jointly to [redacted] co-investigators, the only saliant discussion was with Dr. Quiquempois.

STUDY DESIGN

Protocol FFR/91/486/14, henceforth referred to as Study 14 in this report, covers administration of Mifepristone (RU-486) given as a single dose of 600 mg, followed up by Misoprostol, either once or twice if needed for embryonic expulsion. The time limit limitations for this study are amenorrhea of 49 days or less.

Study FF/92/486/24, henceforth referred to Study 24 in this report, is similar to Study 14, except that amenorrhea is stretched out to 63 days. For each study a second dose of prostiglandin may be administered as necessary for expulsion.

Exhibits 1 and 2 are summaries of Studies 14 and 24, respectively, showing the patient number, birthday, date of consent, dose date, and undesirable effects, among other things. These records

show that for Study 14, the first patient was entered on 7/15/91 and last patient on 12/17/91. For Study 24, the first patient was entered on 12/8/92, with the last patient on 6/22/93.

AUTHORITY AND ADMINISTRATION

The sponsor firm monitor met with [redacted] and explained the nature of the study, and this was formalized in written contract. Excerpts which explained the status of the test article and nature of the protocol and obligations of the clinical investigator are included as exhibits with this report.

Also included as exhibits is a listing of the personnel who were authorized to work on this study. Briefly, these were [redacted], as well as three nurses as listed on exhibit with this report.

The investigator did not discontinue either of the studies before completion, although after completion, the investigator herself relocated and is no longer associated with this facility. The records, however, remain at this clinic in the custody of Dr. Quiquempois.

The Compliance Program requested the names and address of personnel of this facility performing laboratory tests, but this assumes certain conditions not present at this facility. All patients coming into this abortion clinic were referred by their private personal physicians, outside physicians. Therefore, there are corresponding laboratory documents from outside facilities, and there may be literally hundreds. It obviously serves no useful purpose to try to list such outside firms, specific for individual patients, and this was not done. However, outside laboratories may be seen in the exhibits attached with this report.

PROTOCOLS

Included as exhibits are written protocols for each of the studies, including translations from French. The protocols remained unchanged except for an amendment to swell the number of total subjects from 500 to 1,000. This was an all-center number, and when the desired number was reached, the study was stopped.

The protocols as well as the amendments were approved by the suitable Institutional Review Boards (IRB) and as such, approvals are included as exhibits with this report.

SUBJECT RECORDS

In addition to the case record forms (CRF), samples of which are included as exhibits, the records include the patient charts, and all were available for our review. These are in French, naturally, and as usual, the handwriting of the physicians is not easily read. [redacted] deciphered for us difficult passages and inquired of the staff regarding certain shorthand used in the charts.

There is adequate documentation to assure that all audited subjects did exist and were alive and available for the duration of the stated participation in the study, as the charts are complete with full names and addresses. It was not necessary to try to contact any of the participants in this study.

Prior to the inspection, [redacted] was provided with printouts of certain information for both studies, and we compared the information in the printouts and source documents in the patient files. The printouts had been prepared under the direction of the Population Council, the NDA applicant.

The records themselves contain the observations, information and data on the condition of the subject, both pre and post administration, but the problem is that the investigators generally failed to strictly adhere to protocol exclusion requirements. Many patients were entered into the study who should have been ineligible. This is covered in a subsequent heading. There were no study dropouts for either study.

The records for both Study 14 and Study 24 are in the possession of Dr. Quiquempois at this facility, and he reported that he used their practice to maintain such records indefinitely.

OTHER STUDY RECORDS

Attached as exhibits are both handwritten and typed charts for both studies, which list the patient numbers, first three letters of their name, birth dates, consent date, the dose date for the test article, the dose date of the prostiglandin, if done (reviewer will recall that the prostiglandin was administered only if there was no expulsion after a certain time), as well as a column listing whether or not there were any adverse events (non, of course, means "no" and oui means "yes.")

CONSENT OF HUMAN SUBJECTS

Attached as exhibits are copies of consents used for these studies. We found no instances in the records that we reviewed of any missing written informed consent forms.

INSTITUTIONAL REVIEW BOARD

Attached as exhibits with this report are the approvals of the appropriate IRB. The approval was for both the initial protocols, including the consent forms, as well as a separate approval for the extension of one of the studies.

In each case approval was obtained before the start of the studies.

SPONSOR AND MONITORING

This IRB approved the consent form provided by the sponsor.

Attached as exhibits is a listing of monitor visits. It can be seen that there were frequent and regular visits by the study monitors to this facility. The monitors collected documents for submission to the sponsor firm Roussel, which included all documents pertaining to these studies, including IRB approvals.

Even so, one cannot say that it was a stellar job of monitoring, as there was no indication that monitors noted the multiple failures to follow protocol exclusion requirements, as smokers and overage subjects were entered (who should not have been entered into the study), 63 day amenorrhea limit was passed in some instances, and some patients had multiple conditions, any one of which should have ruled them ineligible.

There were laboratory reports missing, ultrasound reports missing, and a failure to notify the sponsor on a timely basis of a serious adverse event. These conditions are detailed in subsequent headings.

TEST ARTICLE ACCOUNTABILITY

The hospital pharmacy was in charge of drug accountability and drug accountability records were checked during this inspection for both studies. Receipt records were complete, dosing records were complete, and no objectionable conditions were noted regarding drug accountability for either study.

RECORDS RETENTION

The sponsor firm Roussel has reportedly copies of the records generated during this study, but the clinic has a complete set of records, both the CRF's and the patient charts. There were no instances of any records missing, although there were instances of individual lab and ultrasound reports that were missing.

FDA-483 OBSERVATIONS AND MANAGEMENT RESPONSE

At the conclusion of the inspection, Form FDA-483, Inspectional Observations, was presented to Dr. H. Quiquempois, Custodian of Records, although it was made out jointly to him and the Co-investigators [redacted] although neither of them was present. [redacted] moved to a different facility and [redacted] was invited not to attend by Dr. Quiquempois. Each point was read to Dr. Quiquempois, although he was fluent in English, and note was taken of his response. This was done in the present of [redacted], our interpreter.

(Studies FFR/91/486/14 and 24)

1. Failure to follow protocol exclusion requirements as follows:

   a. For Study 24, of 116 sets of patient records checked, at least 22 patients entered were smokers (10 or more cigarettes daily for 2 years or more) with smoking history unknown for three others.

      COMMENTS: Actually, we only examined 92 sets of records fairly completely for Study 24. The remaining 24 were checked only to confirm smoking history; thus, the reason for the statement, "116 sets of patient records checked." Those 22 patients were as follows: 65, 70, 74, 77, 83, 89 (there was insufficient information on 90), 93, 97, 98, 101, 104, 106 (there was incomplete information on 108), 111, 112, 116, 119, 723, 745, 747, 749, 980, and 984.

      Some of these records are included as exhibits, and reviewers can see that the records do not agree with themselves, in that the inclusion list may have stated that the person did not smoke and other records stated she was a heavy smoker.

      FIRM'S RESPONSE: Dr. Quiquempois stated his belief that it was a somewhat ambiguous statement for Study 24, which exclusion criteria under

the Section 4.3 states (in English) "The following will not be included: women who . . . are more than 35 years of age and smoke (this criterion will be defined as smoking at lest 10 cigarettes a day for 2-years proceeding the start of the study) . . ."

It was pointed out to Dr. Quiquempois that in the exclusion section where these two are run together, there are separate responses "non" and "oui" for each of these two, even though they appear to run together, and are therefore separate requirements, instead of being limited to those women who are over 35-years of age and do smoke.

b. For Study 24, 48 patients entered of the 190 in the study were over age 35. Of these, two were also smokers, as defined by the protocol.

COMMENTS: Exhibit 2 with this report is the chart that shows among other things, patient numbers and birth dates ("date naissance"). It is a simple matter to see that a considerable number of these ladies were over the 35-year age limit. In case there may have been an error in recording the birth date on these charts, the dates were compared with the hospital records, and in every case they were accurately recorded. Appropriate exhibits are included with this report.

FIRM'S RESPONSE: Dr. Quiquempois stated that there was, "no question of these protocol violations." Reviewers need to remember that it was not he who entered the patient into the study, and these patients were entered on both studies before he became associated with these projects at all.

c. For Study 24, 4 patients of 92 sets of records examined entered into the study were past the 63-day amenorrhea limit. One of these was also over 35 years old, and one was both over 35 and a smoker.

COMMENTS: Appropriate exhibits document this, including Patient 984, the one who was both over 35 and a smoker, and past the 63-day amenorrhea limit. Any one of these should have been enough to rule the subject ineligible for the study.

FIRM'S RESPONSE: Dr. Quiquempois stated that this was certainly possible, and reminded us again that he did not enroll the patients into the study.

d. For Study 14, 7 patients entered were smokers (10 or more cigarettes for 2 years) of 56 sets of patient records checked.

COMMENTS: These are Subject 606, 610, 615, 616, 627, 630, and 754. Appropriate exhibits are included with this report, fully identified in the next heading. Reviewers will recall that Study 14 was done before Study 24.

FIRM'S RESPONSE: Dr. Quiquempois stated that he believes that Roussel, the sponsor firm, intentionally meant to expand the study to include smokers in the second study (Study 24). He stated that Roussel has since decided on 35 years of age, 10 cigarettes, and an amenorrhea not to exceed 7-weeks.

2. Failure to maintain complete and accurate study records as follows:

   a. For Study 14, of 56 sets of patient files checked, 25 had laboratory reports missing or the date reported is in error.

      COMMENTS: Appropriate exhibits of such are included with this report.

      FIRM'S RESPONSE: Dr. Quiquempois stated that the abortion clinic had only been open 2 days a week early on, which he thought might somehow have contributed to that problem.

   b. For Study 14, of 56 sets of patient records checked, 21 had ultrasound records missing or the date reported is in error. For Study 24, of 92 sets of patient records checked, 3 ultrasound records were missing or the date reported is in error.

      COMMENTS: Appropriate exhibits are included with this report.

      FIRM'S RESPONSE: There were more records missing from the first study, Study 14, than from the second study, where only 3 ultrasound records were missing or the day reported is in error.

      Dr. Quiquempois reminded us that Study 14 had been done first and perhaps that was the reason; that the people involved with these studies learned something from the first study and had fewer errors on Study 24.

3. Failure to follow protocol requirements to notify the sponsor Roussel within 24-hours of a serious adverse event, such as the 23 April, 1993 notification of Patient 751's hospitalization and transfusions on February 9-11, 1993.

   COMMENT: These records are included as exhibits with this report.

Dr. Quiquempois stated that it was possible that if another hospital did the work, which was the usual situation for follow-up work, that reporting might have been delayed, but he did agree that 2-months was an unreasonable time to extend a 24-hour protocol reporting requirement.

Nevertheless, [redacted] did tell Dr. Quiquempois that notwithstanding these objectionable conditions, he would not recommend that the study not be accepted in support of the pending NDA.

EXHIBITS

Exhibit 1	Summary charts, all patients, Study 14.
Exhibit 2	Summary chart, all patients, Study 24.
Exhibit 3	Handwritten chart, inclusion dates.
Exhibit 4	Protocol FFR/91/486/14.
Exhibit 5	Protocol FF/92/486/24.
Exhibit 6	Information for the Patient, Stuay 14 and Study 24.
Exhibit 7	Protocol amendment, Study 14, swelling the numbers from 500 to 1,000.
Exhibit 8	IRB approval with IRB membership list, with specialties (same IRB as granted approval to sister site, Dr. Aubeny in Paris.)
Exhibit 9	Statement of Investigator, equivalent documents with a listing of personnel involved in this study.
Exhibit 10	Monitoring visits' assessment list, with notification of intent to audit, and listing of dossiers to be selected for audit.
Exhibit 11	Excerpts of printout for Study 14, supplied by Population Council.
Exhibit 12	Selected printouts, Study 24, supplied by Population Council.
Exhibit 13	Chart used by doctors to estimate days of the amenorrhea.

Exhibit 14 — Excerpts from Table 11 and Table 15 of NDA regarding adverse events, Subject 751 (see also records Exhibit 18).

Exhibit 15 — Excerpts of records for Subject 1194, overage and heavy smoker.

Exhibit 16 — CRF excerpts for Subject 1015, overage.

Exhibit 17 — Record excerpts for Subject 984, heavy smoker, aspiration needed.

Exhibit 18 — Record excerpts for Subject 751, overage, adverse event requiring transfusions.

Exhibit 19 — Record excerpts for Subject 729, with CRF showing empty uterus, but a pelvic echograph showing persistent signs of intra uterine retention.

Exhibit 20 — Record excerpts for Subject 95, compare CRF complete expulsion date of December 31, 1992, with ultrasound findings January 11, 1993.

Exhibit 21 — Record for Subject 94 and corresponding echograph.

Exhibit 22 — CRF page for Subject 89 showing that she does not smoke, and corresponding intake interview saying she smoked 30-40 cigarettes a day for 15 years.

Exhibit 23 — Excerpt records for Subject 70, overage, heavy smoker.

Exhibit 24 — Record excerpts for Subject 65, heavy smoker.

Exhibit 25 — Record excerpts for Subject 64, overage.

Exhibit 26 — Excerpt records for Subject 63, adverse event, hemorrhage requiring curettage.

Exhibit 27 — These are record excerpts for Patient 61 of Study 24, showing retention of "deciduale" on the ultrasound of December 16, 1992, per printout which is part of Exhibit 12 with this report and shows a date and time of expulsion 6-days earlier.

Exhibit 28 — These are excerpts from Patient 2101 oF Study 14, which show that ultrasound reports and photos do not match.

Exhibit 29 Excerpts from Patient 2257 of Study 14, which are in disagreement from the ultrasound report and the conclusions of the case study.

Exhibit 30 These are excerpts from Patient 1468 from Study 14 records showing a disagreement between the ultrasound, which says there is an image of retention of trophoblasts, and the patient's CRF states that the uterus is empty based on the same echograph on January 15, 1992.
This patient was a no show for the followup, but did telephone that the ultrasound and report were to be sent. They were and are attached, and it is on these that the doctor made the conclusion that the uterus was empty, even though that was not the conclusion of the expert, a [redacted] who read the echogram.

Exhibit 31 These are excerpts from Patient 602 of Study 24, and reviewers should also look at the printout for this page which is part of Exhibit 11. There are adverse reactions shown on the printout; however, the records indicate that there was an aspiration on [redacted] Following this aspiration on [redacted] there was an echogram of August 28, 1991, indicating that she was again pregnant with RU-486, again administered on September 5, 1991, but with another aspiration necessary on [redacted]

This "super woman" as she is referred to in the files, was not part of the study on this second go around. This was possible because the drug was available and on the market in France at this time.

Exhibit 32 These are record excerpts from Patient 629 of Study 14, CRF's and hospital chart, which show a retention, which was not noted in the Population Council-supplied printout for this patient, which is part of Exhibit 11.

Exhibit 33 Records for Patient 755 of Study 14 show discrepancies between laboratory dates and the CRF lab dates.

Exhibit 34 These are excerpts of records for Patient 754 of Study 14, which show she smoked too much to be included in the study, and lab dates do not agree with the information listed for this patient on the Population Council-supplied printouts, part of Exhibit 11.

Exhibit 35 Records for Patient 630 of Study 14 show that she is a heavy smoker and should have been ineligible, although her CRF states she does not smoke enough to be excluded.

Exhibit 36 Records for Patient 606 of Study 14 show that she is too heavy a smoker to be included in this study, although the exclusion page of the CRF accepts her.

Exhibit 37 Patient 1463 of Study 14 has records showing disagreement between the case record form and the laboratory report for dates, and the conclusions on Page 12 of the CRF are dated 12/26/91, for echograph, showing an empty uterus, but the echograph's are not taken until 4-days later as confirmed by both the pictures and the written report

/S/

Dallas District

Clinical Investigation Branch
CDER (HFD-344)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Dr. H. Quiquempois, Custodian of Records	PERIOD OF INSPECTION 1 to 5 July	C. F. NUMBER 1996
TITLE OF INDIVIDUAL CoInvestigators	TYPE ESTABLISHMENT INSPECTED Clinical Investigators	
FIRM NAME Centre Hospitalier de Valenciennes, Unite d'Orthogenie	NAME OF FIRM, BRANCH OR UNIT INSPECTED $same?	
STREET ADDRESS Avenue Desandrouin B.P. 479, 59322 Valenciennes, France	STREET ADDRESS OF PREMISES INSPECTED	
CITY AND STATE (Zip Code) 59322 Valenciennes, France	CITY AND STATE (Zip Code)	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

(Studies FFR/91/486/14 and 24)

1. Failure to follow protocol exclusion requirements.

   a. For study 24, of 116 sets of patient records checked, at least 22 patients entered were smokers (10 or more cigarettes daily for two years or more) with smoking history unknown for three others.

   b. For study 24, 48 patients entered of the 190 in the study were over age 35. Of these, two were also smokers, as defined by the protocol.

   c. For study 24, 4 patients of 92 sets of records examined entered into the study were past the 63 day amenorrhea limit. One of these was also over 35 years old, and one was both over 35 and a smoker.

   d. For study 14, 7 patients entered were smokers (10 or more cigarettes for two years) of 56 sets of patient records checked.

2. Failure to maintain complete and accurate study records.

   a. For study 14; of 56 sets of patient files checked, 25 ~~61~~ had laboratory reports missing or the date reported is in error. ~~For study 24, of 92 sets of patient records checked, 3 ultrasound records were missing or the date reported is in error.~~ 51

3. Failure to follow protocol requirements to nofify the sponsor Roussel within 24 hours of a serious adverse event, such as the 23 April, 1993 notification of patient —751's hospitalization and transfusions on

2.b. ~~For~~ study 14, of 56 sets of patient records checked, 21 had ultrasound records missing or the date reported is in error. For study 24, of 92 sets of patient records checked, 3 ultrasound records were missing or the date reported is in error.

/S/

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/	EMPLOYEE(S) NAME AND TITLE (Print or Type) Investigator	DATE ISSUED 5 July 1996

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 1 OF 1 PAGES

MIF 004039

4143

Clinical Investigator or Sponsor:

Routine ☒ - P/C ☐ Biopharm. ☐ H. Quinquempois

CIB

DATE	TO	ACTION REQUESTED
11/20/96	—	
12/23	—	QUIQUIMPO.CDT
12/24	—	
1/14	—	
Jan 17	—	OK
1/17		

APPEARS THIS WAY
ON ORIGINAL

ROUSSEL LABORATORIES
MEDICAL MANAGEMENT

MAY 1991

Translation from French

EFFICACY AND TOLERANCE OF MIFEPRISTONE (RU 486) ADMINISTERED IN A SINGLE DOSE OF 600 mg IN ASSOCIATION WITH MISOPROSTOL AS AN ALTERNATIVE FOR VACUUM ASPIRATION FOR TERMINATION OF PREGNANCY WITH AMENORRHEA OF 49 DAYS OR LESS

Protocol No. FFR/91/486/14

(Mifepristone - Misoprostol)

Circled item indicate those ________________ ________________ for Aubery, ________ (Quinquempois) and ________ clinics.

Number of container with Mifepristone : |___|___|___|___|___|

Place the removable label from Mifepristone container here:

Valenciennes. France
7-15-96
EXH. 4

Protocol FFR/91/486/14 with Case Record Forms

NDA 20-687

Volume 1.31

Pages 300 - 342

APPEARS THIS WAY
ON ORIGINAL

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

Study Phase: III

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

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

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

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

Concurrent Control: None

Estimated Total Sample Size: 1000
Statistical Rationale Provided: No

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

Adverse Reactions: Volunteered

Plan for Data Analysis: No

APPEARS THIS WAY
ON ORIGINAL

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

(Original Language Document is located in Appendix D1)

APPEARS THIS WAY
ON ORIGINAL

ROUSSEL Laboratories
Medical Division

Protocol FFR/91/486/14

APPEARS THIS WAY
ON ORIGINAL

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

May 1991

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

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APPENDICES:

APPEARS THIS WAY
ON ORIGINAL

1. INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

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

2. PURPOSE OF THE STUDY

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

3. DESCRIPTION OF THE STUDY

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

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

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

4. CHOICE OF SUBJECTS

4.1 Number

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

4.2 Inclusion Criteria

The following will qualify for inclusion: women who

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

and whose pregnancy is:

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

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

4.3. Exclusion Criteria

The following will not qualify for inclusion: women who

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

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

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

5. TREATMENT

5.1 Mifepristone

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

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

The boxes of mifepristone will be labeled as follows:

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

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

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

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

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

5.2. Prostaglandin Analog

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

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

5.3 Combined Treatments

5.3.1 Authorized treatments

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

Treatments in progress will be indicated in the observation notebook.

5.3.2 Prohibited Treatments

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

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

- The patient must refrain from self-medication.

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

6. EVALUATION CRITERIA

6.1 Efficacy

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

A distinction will be made between:

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

2) Interruption of pregnancy without complete expulsion.

3) Persistent pregnancy.

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

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

6.2 Safety

6.2.1. When misoprostol is administered (day 3):

Safety will be evaluated on:

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

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

Safety will be evaluated based upon:

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

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

6.2.3 Biological Safety

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

7.1 Initial Evaluation (day 1)

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

- Record:

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

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

- Measure the bHCG and do a uterine ultrasound.

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

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

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

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

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

7.2. Day 3: Administration of Misoprostol:

- Clinical examination

- Look for any adverse effect.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- Note the results of the hemoglobin measurement.

8. DATA COLLECTION AND ANALYSIS

8.1. Data collection:

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

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

8.2. Data analysis:

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

9 AMENDMENTS TO THE PROTOCOL

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

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

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

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

10. SIDE EFFECTS AND ADVERSE EVENTS

10.1. Serious Adverse Event:

A serious adverse event is defined as:

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

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

- any event necessitating hospitalization or extension of hospitalization,

- discovery of a congenital anomaly or a cancer.

- an overdosage.

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

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

OR

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

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

10.2 Benign adverse events.

These will only be reported in the case report form.

11. PATIENTS LOST TO FOLLOW-UP AND DISCONTINUED FROM THE TRIAL

Each patient entered in the study will be analyzed for safety. Only those women who have completed the trial will be able to be analyzed for efficacy.

12. NOTIFICATION OF AUTHORITIES

The Minister of Health will be informed of the study.

13. ETHICS

This study will be conducted according to the principles of the Declaration of Helsinki (see Appendix 3) and according to French laws governing clinical trials.

13.1 Consent

Before inclusion of a patient in the study, her written consent will be obtained (signed by the patient and preceded by the statement "read and approved".) In order to obtain her consent, she will be provided with a document containing information on the study in which she has been asked to take part.

In addition, the investigator will sign an "identification and obtaining of consent" form, "thus attesting that the patient's consent has indeed been obtained".

13.2 Ethical Committee:

The protocol will be submitted to an Ethical Committee.

The study will begin only after Roussel Laboratories has received a copy of the committee's written agreement.

In the case of a protocol amendment, this amendment will have to be submitted to and approved by the Ethical Committee, if it is likely to alter the relationship between the patients' medical benefit and risks in an unfavorable manner.

14. CONFIDENTIALITY

The data collected during this study will be considered confidential.

The information provided by Roussel Laboratories (product brochure, protocol, case report form) are likewise 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 on this study must be kept available to the other investigators participating in it, the Roussel Laboratories Coordinator, the Quality Control Officer, the Ethics Committee, and the Overseeing Authorities.

15. STUDY FOLLOW-UP AND QUALITY CONTROL

The members of the Roussel Laboratory will be in regular contact with the investigator by on-site visits and telephone calls to monitor the progress of the study and make sure that it is conducted pursuant to the protocol.

The observation notebooks will be reviewed in detail during each visit.

The investigator and his/her team agree to cooperate with the monitor, and specifically to furnish any missing documents and information whenever possible.

Each observation notebook will be signed by the investigator, who must initial and date all corrections.

If data is missing or unavailable, the reason will be stated.

The participation in this study means that the investigator accepts the possibility of a quality control audit to verify that the procedures described in the protocol have been followed throughout the study.

16. DURATION OF STUDY

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

17. INSURANCE

The investigator's civil liability, under this study, is covered by insurance purchased by the Roussel Laboratories (appendix 4).

18. PUBLICATION

Any presentation or publication of the results of this study must first be the subject of an agreement between the investigators and the Roussel Laboratories.

19. INVESTIGATOR'S LIABILITY AND UNDERTAKING

All the information on the product tested and the results of the study are considered to be confidential.

I have read the protocol and I feel that it contains all the information necessary for conducting the trial.

I undertake to conduct this trial pursuant to the protocol; I will not make any modification to to the trial without the written agreement of the Roussel Laboratories.

I undertake not to start the study until an Ethics Committee has given its agreement.

I will conduct this trial according to the principles set forth in the Helsinki Statement, and in conformity with Good Clinical Practice; specifically, I will obtain the informed consent of each patient before they enter the study.

I further undertake to carefully fill in the observation notebooks, to respect the procedure in the event of serious side effect and to monitor the management of the product under experimentation.

I agree to the monitoring of the study by a member of Roussel Laboratories and to the outcome of a quality control audit.

I will keep all information directly concerning the study available to the Roussel Laboratories and the Overseeing Authorities.

I will retain the gross data collected in this study for a period of 10 years.

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

Date — Signature of Investigator

Date — Signature of Roussel Laboratories Coordinator

REFERENCES

1. Investigator Drug Brochure

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.ULMAN - Utilization of Mifepristone in the Voluntary interruption of pregnancy. French Experiment. Presse Med., 1989, 18, p. 757-760.

5. L. SILVESTRE, C. DUBOIS, M. RENAULT, Y.REZVANI, E.E. BAULIEU, A. ULMAN - 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 38 486 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. Report on study FFR/88/486/01 (ROUSSEL Laboratories)

9. E. FLIERS, 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. 475-545.

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 - Contraceptive effect of combining RU 486 with an active prostaglandin by mouth. C.R. Acad. Sci., Paris (in press).

CHECK-LIST

DAY 1: INCLUSION:

- Confirmed pregnancy, progressing normally,

- Clear request for voluntary interruption of pregnancy, legal measures taken,

- Amenorrhea less than or equal to 49 days,

- Age over 18 years (or authorization from legal guardian for minors) and less than or equal to 35 years,

- No contraindication for the method,

- Explain to the patient what happens in a miscarriage and the modalities of the protocol, and obtain her informed consent,

- Measure bHCG and/or ultrasound,

- Measure hemoglobin, blood group,

- Administer 600 mg (three 200 mg tablets) of mifepristone in a single administration in the investigator's presence,

- Tell the patient that she must not smoke or drink alcohol for the next 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,

- Note any functional signs that appear after administration of Mifepristone,

- Verify that expulsion did not occur between day 1 and day 3,

- If no expulsion has occurred, administer misoprostol: two 0.2 mg tablets in a single administration,

- Observance for 4 hours following that administration:

  · Every hour measure the heart rate, systolic and diastolic blood pressure,

  · Watch for any painful uterine contractions, nausea, vomiting, diarrhea, evaluate their intensity and record any treatments administered,

- Appointment for day 8 - day 15, with prescription for hemoglobin measurement just before the next visit

CHECK-LIST

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

DAY 8 - DAY 15: FOLLOW-UP VISIT:

- Evaluate the efficacy and safety of the treatment,

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

- Note the results of the hemoglobin measurement.

- In the event of failure (ongoing pregnancy or uterine retention), recommend an additional surgical procedure.

AMENDMENT TO PROTOCOL FFR/91/486/14

(with regard to the May 1991 version)

"Efficacy and safety of mifepristone (RU 486)
at the dose of 600 mg in a single administration in combination
with misoprostol as an alternative to uterine aspiration
for interruption of pregnancy aged less than or equal
to 49 days of amenorrhea"

Ø NUMBER OF SUBJECTS

Page 3, paragraph 4.1, the anticipated number of patients is 1,000 instead of 500.

Ø STUDY FOLLOW-UP

After the end of the study of the anticipated 1,000 patients, the research centers that so desire may continue the study. The study shall be continued pursuant to the same protocol, except for the following points:

- the number of subjects shall not be defined; the study shall be stopped as soon as the Marketing Authorization has been obtained for the mifepristone-misoprostol combination.
- elimination of the hemoglobin rate measurements on day 1 and day 8-day 15 (paragraphs 6.2.3, page 7 eliminated).
- a simplified observation notebook will be filled in for each patient.

DATE:

For the investigator For the sponsor

ROUSSEL LABORATORIES
MEDICAL MANAGEMENT

MAY 1991

Translation from French

EFFICACY AND TOLERANCE OF MIFEPRISTONE (RU 486) ADMINISTERED IN A SINGLE DOSE OF 600 mg IN ASSOCIATION WITH MISOPROSTOL AS AN ALTERNATIVE FOR VACUUM ASPIRATION FOR TERMINATION OF PREGNANCY WITH AMENORRHEA OF 49 DAYS OR LESS

Protocol No. FFR/91/486/14

(Mifepristone - Misoprostol)

Number of container with Mifepristone : |___|___|___|___|

Place the removable label from Mifepristone container here:

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF # |0212|

Center |_|_|_|_|_| 5

Subject |_|_|_|_| 10

INCLUSION CRITERIA

(mark correct answer)

The patient must answer YES to all of the following questions in order to be included in this study.

Patient:

- requests termination of pregnancy — No___ Yes___
- satisfies the legal requirements associated with voluntary termination of pregnancy under French law — No___ Yes___
- is of 18 years of age (or has parental consent) and is not older than 35 years of age — No___ Yes___
- has an intrauterine pregnancy of known duration of less than or equal to 49 days of amenorrhea — No___ Yes___
- is accepting surgical termination of pregnancy in case of treatment failure — No___ Yes___
- agrees to comply with the constraints of the study — No___ Yes___
- is informed about the nature of study and willing to give her written consent to participate — No___ Yes___

APPEARS THIS WAY
ON ORIGINAL

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF # |0199| 1 Center |_|_|_|_|_| 5 Subject |_|_|_|_| 10

EXCLUSION CRITERIA

(mark correct answer)

The patient must answer NO to all of the following questions in order to be included in this study.

Patient:

-shows signs of threatened abortion	No___	Yes___
-has suspicion of ectopic pregnancy	No___	Yes___
-has amenorrhea of more than 49 days	No___	Yes___
-has adrenal deficiency	No___	Yes___
-has been treated for chronic corticoid in the past 6 months	No___	Yes___
-has renal or liver deficiency	No___	Yes___
-has known thrombosis or receiving treatment for blood clots	No___	Yes___
-has evidence of the presence of: asthma, cardiovascular disease (angina pectoris, arrhythmia, cardiac failure, valvular disease, hypertension), glaucoma, diabetes, hyperlipidemia	No___	Yes___
-is older than 35 years of age	No___	Yes___
-is a smoker (smoking a minimum of at least 10 cigarettes per day for 2 years preceding start of study)	No___	Yes___
-has known allergy to Mifegyne	No___	Yes___
-has anemia	No___	Yes___

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF #	Center	Subject
|0199| 1	|__|__|__|__|__| 5	|__|__|__|__| 10

EXCLUSION CRITERIA

(mark correct answer)

-is unlikely to comply with the protocol requirements or is living far away from the medical center	No___	Yes___
-refuses to give a written consent to participate	No___	Yes___

APPEARS THIS WAY ON ORIGINAL

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF # |0213| 1 Center |__|__|__|__|__| 5 Subject |__|__|__|__| 10

INITIAL VISIT (Day 1)

1. PATIENT

Last Name (first 3 letters) |__|__|__|

First name |__|__|__|__|__|__|__|__|

Date of birth (dd/mm/yy) |__|__|/|__|__|/|__|__|

Weight (kg) |__|__|__|

Height (cm) |__|__|__|

2. MEDICAL HISTORY

_____

_____

_____

Presently receiving treatment(s)? No___ Yes___

if YES:

NATURE		REASON	
_____		_____	
_____		_____	
_____		_____	

CRF # |0213| 1 Center |__|__|__|__|__| 5 Subject |__|__|__|__| 10

INITIAL VISIT (Day 1)

3. CURRENT PREGNANCY

- FIRST DAY OF THE LAST MENSTRUAL PERIOD |___|/|___|/|___|
  dd / mm / yy

- ULTRASOUND SCAN - GESTATIONAL AGE |__|__|
  (days of amenorrhea)

OR

- Rate of βHCG Date taken (most recent, prior to Day 1) |___|/|___|/|___|
  dd / mm / yy

VALUE |_____| UNITS_____

Value higher than normal in absence of pregnancy |_____|

4. THERAPY SCHEDULE

DOSE OF MIFEGYNE (3 tablets x 200 mg in one uptake)

DATE |___|/|___|/|___| TIME |____|:|____|

Note the number of the container of Mifegyne (4 digits)
on the cover page of this study.

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF # |0201| 1 Center |__|__|__|__|__| 5 Subject |__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (Day 3)

1. WAS PATIENT EXPERIENCING ANY ADVERSE EFFECTS BETWEEN THE ADMINISTRATION OF MIFEGYNE AND THE ADMINISTRATION OF MISOPROSTOL? No___ Yes___

   If YES, report all symptoms on page 14

2. DOSE OF MISOPROSTOL (2 tablets in one dose)

   DATE |___|/|___|/|___| dd / mm / yy TIME |___|:|___|

3. IF MISOPROSTOL WAS NOT ADMINISTERED

   specify reason:

   Expulsion occurred prior to day 3: No___ Yes___

   If NO, specify reason for not administering:

   _____

   _____

   _____

APPEARS THIS WAY
ON ORIGINAL

CRF # |0209| 1 Center |__|__|__|__|__| 5 Subject |__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (Day 3)

4 - RESPONSE TO TREATMENT

Observation at the Center is required during the 4 hours following administration of MISOPROSTOL

4.1 VITAL SIGNS

	0 HR	1HR	2HR	3HR	4HR
Systolic blood pressure (mm Hg)	|__|	|__|	|__|	|__|	|__|
Diastolic blood pressure (mm Hg)	|__|	|__|	|__|	|__|	|__|
Heart rate (per minute)	|__|	|__|	|__|	|__|	|__|

If patient experiences thoracic pain, immediately perform an EKG and administer nitro-compound. Inform Roussel Laboratories at once.

APPEARS THIS WAY ON ORIGINAL

CRF # |0214| 1 Center |__|__|__|__| 5 Subject |__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (Day 3)

4.2 - PAINFUL CONTRACTIONS OF UTERUS No___ Yes___

If YES, severity: |___|

1=mild
2=moderate
3=severe, no treatment required
4=severe, requiring treatment

If treatment(s) required, specify:

NAME	DOSE	ROUTE
_____ |___| _____ |___| _____ |___|
_____ |___| _____ |___| _____ |___|
_____ |___| _____ |___| _____ |___|

PREMEDICATION TAKEN No____ Yes__
(Not-automatic, is left up to discretion of investigator before administering Misoprostol)

If YES, specify:

NAME	DOSE	ROUTE
_____ |___| _____ |___| _____ |___|
_____ |___| _____ |___| _____ |___|
_____ |___| _____ |___| _____ |___|

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF #	Center	Subject
|0215| 1	|__|__|__|__|__| 5	|__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (Day 3)
VISUAL ANALOG SCALE

To be performed on patient 4 hours after dispensing Misoprostol
by asking the following:

"Please describe the general intensity of the pain which you experienced?"

TIME OF MEASURE |____|:|____|
hh mm

MEASURE (leave box blank) |_____|

SCALE OF PAIN

NO PAIN — UNBEARABLE PAIN

|_____|

How to mark: Indicate evaluation of pain by placing vertical line on the scale

Example:

NO PAIN — UNBEARABLE PAIN

|_____|_____|

CRF # |0204| | Center |__|__|__|__|__| 5 | Subject |__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (D3)

4.3 - NAUSEA AND VOMITING

NAUSEA No___ Yes___

If YES, severity |__|

1=mild
2=moderate
3=severe, no treatment required
4=severe, treatment required

VOMITING No___ Yes___

If YES, severity |__|

1=mild
2=moderate
3=severe, no treatment required
4=severe, treatment required

If treatment for nausea or vomiting was required, specify:

NAME	DOSE	ROUTE
_____	_____(8)	_____
|__|__|__|		|__|
_____	_____(8)	_____
|__|__|__|		|__|

CRF # |0216| 1 Center |__|__|__|__|__| 5 Subject |__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (D3)

4.4 - DIARRHEA No___ Yes___

If YES, severity: |__|

1=mild
2=moderate
3=severe, no treatment required
4=severe, treatment required

If treatment was required, specify:

NAME	DOSE	ROUTE
_____ |__|__|	_____(8)	_____ |__|
_____ |__|__|	_____(8)	_____ |__|

4.5 - OTHER ADVERSE EXPERIENCE No___ Yes___

If YES, report symptoms on page 14

5 - SUMMARY OF THE MONITORING PERIOD

Did expulsion occur during observation at the center? No_____ Yes_____

If YES, report day and time on page 12

Any comments regarding the monitoring period

_____

_____ |__|__|

CRF # |0217| 1 Center |__|__|__|__|__| 5 Subject |__|__|__|__| 10

FOLLOW UP VISIT (D8 - D15)

DATE of the VISIT |__|__|/|__|__|/|__|__| dd / mm / yy

1 - RESULT OF TREATMENT |__|

1=termination of pregnancy, complete expulsion
2=termination of pregnancy, ovule or placenta retained
3=ongoing pregnancy
4=surgical procedure for hemostatic indication (to stop bleeding)

IN CASE PREGNANCY IS TERMINATED AND EXPULSION COMPLETED:

Date of ovular expulsion |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hr : mn

IF EXPULSION DID NOT OCCUR, ONGOING PREGNANCY OR SURGICAL PROCEDURE FOR HEMOSTATIC INDICATION:

Date of surgical procedure |__|__|/|__|__|/|__|__| dd / mm / yy

Nature: |__|

1=endo-uterine aspiration
2=uterine revision
3=other, specify _____ |_____|

Rate of βHCG Date |__|__|/|__|__|/|__|__|

Value |_____| Units _____

Value higher than normal in the absence of pregnancy |_____|

Ultrasound Date: |__|__|/|__|__|/|__|__|

Results (in plain language)_____
_____

Roussel Laboratories

STUDY: FFR/91/486/14

Product: RU38486

CRF # |0217| | Center |__|__|__|__|__| 5 | Subject |__|__|__|__| 10

FOLLOW-UP VISIT (Day 8 - Day 15)

2 - TOLERANCE

2.1 - UTERINE BLEEDING No___ Yes___

If YES:

DATE bleeding STARTED |__|__|/|__|__|/|__|__| dd / mm / yy

TOTAL DURATION of bleeding (in days) |__|__|

DUE TO BLEEDING IS IT NECESSARY:

- to test concentration of hemoglobin No___ Yes___

If YES, date of test |__|__|/|__|__|/|__|__|

Value (g/dl) |__|__|.|__|

- a transfusion No___ Yes___

If YES, number of units of packed red cells |__|__|

- medical treatment No___ Yes___

If YES, what kind_____

2.2 - ANY ADVERSE EVENT OTHER THAN UTERINE CONTRACTIONS, NAUSEA, VOMITING OR DIARRHEA DURING THE 4 HOURS FOLLOWING MISOPROSTOL No___ Yes___

If YES, report symptoms on page 14.

3. STARTED TAKING ORAL CONTRACEPTIVE BEFORE THIS FOLLOW-UP VISIT No___ Yes___

If YES - Date Started |__|__|/|__|__|/|__|__|

Name of the product _____ |__|__|

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF # |0207| 1 Center |__|__|__|-|__|5 Subject |__|__|__|__|10

ADVERSE EVENTS - SYMPTOMS

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

NATURE OF THE SYMPTOM_____

START DATE |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hh mn

STOP DATE |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hh mn

SEVERITY 1=mild, 2=moderate, 3=severe |__|

RELATED TO THE MIFEPRISTONE TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

RELATED TO THE MISOPROSTOL TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

ACTION REQUIRED? No___ Yes___

If YES, specify_____
_____

OUTCOME OF EXPERIENCE

|__| Recovered
|__| Side-effects, specify_____
|__| Died
Date (dd/mm/yy) |__|__|/|__|__|/|__|__|

Could be treatment related No___ Yes___

COMMENTS_____
_____

In case of a serious adverse event, the investigator should immediately contact the authorities at Roussel Laboratories by telephone.

Roussel Laboratories -

STUDY : FFR/91/486/14

Product: RU38486

CRF # Center Subject

|0207| 1 |__|__|__|__|__| 5 |__|__|__|__| 10

ADVERSE EVENTS - SYMPTOMS

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

NATURE OF THE SYMPTOM_____

START DATE |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hh mn

STOP DATE |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hh mn

SEVERITY 1=mild, 2=moderate, 3=severe |__|

RELATED TO THE MIFEPRISTONE TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

RELATED TO THE MISOPROSTOL TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

ACTION REQUIRED? No___ Yes___

If YES, specify_____

_____

OUTCOME OF EXPERIENCE

|__| Recovered
|__| Side-effects, specify_____
|__| Died
Date (dd/mm/yy) |__|__|/|__|__|/|__|__|

Could be related to treatment No___ Yes___

COMMENTS_____

_____

In case of a serious adverse event, the investigator should immediately contact the authorities at Roussel Laboratories by telephone.

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF # |0207| 1 Center |__|__|__|__| 5 Subject |__|__|__|__| 10

ADVERSE EVENTS - SYMPTOMS

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

NATURE OF THE SYMPTOM_____

START DATE |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hh mn

STOP DATE |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hh mn

SEVERITY 1=mild, 2=moderate, 3=severe |__|

RELATED TO THE MIFEPRISTONE TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

RELATED TO THE MISOPROSTOL TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

ACTION REQUIRED No___ Yes___

If YES, specify_____

_____

OUTCOME OF EXPERIENCE

|__| Recovered
|__| Side-effects, specify_____
|__| Died
Date (dd/mm/yy) |__|__|/|__|__|/|__|__|

Could be related to treatment No___ Yes___

COMMENTS_____

_____

In case of a serious adverse event, the investigator should immediately contact the authorities at Roussel Laboratories by telephone.

Roussel Laboratories

STUDY : FFR/91/486/14

Product: RU38486

CRF # |0218| 1 Center |__|__|__|__| 5 Subject |__|__|__|__| 10

HEMOGLOBIN RATE

	D 1 (before taking Mifepristone)	D8 - D15 Follow up visit
DATE taken (dd/mm/yy)	|__|/|__|/|__|	|__|/|__|/|__|
HEMOGLOBIN (g/dl)	|__|:|__|	|__|:|__|

CONCLUSION

Are there any DEVIATIONS FROM THE PROTOCOL? No___ Yes___

If YES, specify _____

_____

_____ |__|

REASONS for deviation:

ANY OTHER COMMENTS:

NAME of Investigator _____ SIGNATURE (obligatory) STAMP (obligatory)

Roussel Laboratories
STUDY : FFR/91/486/14
Product: RU38486

CRF # |0212|

Center |__|__|__|__|__|5

Subject |__|__|__|__|10

INCLUSION CRITERIA

(mark correct answer)

The patient must answer YES to all of the following questions in order to be included in this study.

Patient:

- requests termination of pregnancy — No___ Yes___
- satisfies the legal requirements associated with voluntary termination of pregnancy under French law — No___ Yes___
- is of 18 years of age (or has parental consent) and is not older than 35 years of age — No___ Yes___
- has an intrauterine pregnancy of known duration of less than or equal to 49 days of amenorrhea — No___ Yes___
- is accepting surgical termination of pregnancy in case of treatment failure — No___ Yes___
- agrees to comply with the constraints of the study — No___ Yes___
- is informed about the nature of study and willing to give her written consent to participate — No___ Yes___

He will check signing date on site

CRF # 0199 | Center – |__|__|__|__|__| 5 | Subject |__|__|__|__| 10

EXCLUSION CRITERIA
(mark correct answer)

The patient must answer NO to all of the following questions in order to be included in this study.

Patient:

-shows signs of threatened abortion	No___	Yes___
-has suspicion of ectopic pregnancy	No___	Yes___
-has amenorrhea of more than 49 days	No___	Yes___
-has adrenal deficiency	No___	Yes___
-has been treated for chronic corticoid in the past 6 months	No___	Yes___
-has renal or liver deficiency	No___	Yes___
-has known thrombosis or receiving treatment for blood clots	No___	Yes___
-has evidence of the presence of: asthma, cardiovascular disease (angina pectoris, arrhythmia, cardiac failure, valvular disease, hypertension), glaucoma, diabetes, hyperlipidemia	No___	Yes___
-is older than 35 years of age	No___	Yes___
-is a smoker (smoking a minimum of at least 10 cigarettes per day for 2 years preceding start of study)	No___	Yes___
-has known allergy to Mifegyne	No___	Yes___
-has anemia	No___	Yes___

CRF # |0199| 1 Center |__|__|__|__|__| 5 Subject |__|__|__|__| 10

EXCLUSION CRITERIA

(mark correct answer)

-is unlikely to comply with the protocol requirements or is living far away from the medical center No___ Yes___

-refuses to give a written consent to participate No___ Yes___

Roussel Laboratories
STUDY : FFR/91/486/14
Product: RU38486

CRF # |0213| 1 Center |__|__|__|__| 5 Subject |__|__|__|__| 10

INITIAL VISIT (Day 1)

1. PATIENT

Last Name (first 3 letters) |__|__|__|

First name |__|__|__|__|__|__|__|__|

Date of birth (dd/mm/yy) |__|__|/|__|__|/|__|__|

Weight (kg) |__|__|__|

Height (cm) |__|__|__|

2. MEDICAL HISTORY

_____

_____

_____

Presently receiving treatment(s)? No___ Yes___

if YES:

NATURE	REASON
_____ |_____|	_____ |_____|
_____ |_____|	_____ |_____|
_____ |_____|	_____ |_____|

CRF # |0213| | Center |__|__|__|__|5 | Subject |__|__|__|__|10

INITIAL VISIT (Day 1)

3. CURRENT PREGNANCY

- FIRST DAY OF THE LAST MENSTRUAL PERIOD |__|__|/|__|__|/|__|__|
dd / mm / yy

- ULTRASOUND SCAN - GESTATIONAL AGE |__|__|
(days of amenorrhea)

OR

- Rate of βHCG Date taken (most recent, prior to Day 1) |__|__|/|__|__|/|__|__|
dd / mm / yy

VALUE |_____| UNITS_____

Value higher than normal in absence of pregnancy |_____|

4. THERAPY SCHEDULE

DOSE OF MIFEGYNE (3 tablets x 200 mg in one uptake)

DATE |__|__|/|__|__|/|__|__| TIME |__|__|:|__|__|

Note the number of the container of Mifegyne (4 digits)
on the cover page of this study.

CRF # |0201| Center |__|__| Subject |__|__|__|__|

ADMINISTRATION OF MISOPROSTOL (Day 3)

1. WAS PATIENT EXPERIENCING ANY ADVERSE EFFECTS BETWEEN THE ADMINISTRATION OF MIFEGYNE AND THE ADMINISTRATION OF MISOPROSTOL? No___ Yes___

   If YES, report all symptoms on page 14

2. DOSE OF MISOPROSTOL (2 tablets in one dose)

   DATE |___|/|___|/|___| TIME |___|:|___|
   dd / mm / yy

3. IF MISOPROSTOL WAS NOT ADMINISTERED

   specify reason:

   Expulsion occurred prior to day 3: No___ Yes___

   If NO, specify reason for not administering:

CRF # 0209 | Center |__|__|__| 5 | Subject |__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (Day 3)

4 - RESPONSE TO TREATMENT

Observation at the Center is required during the 4 hours following administration of MISOPROSTOL

4.1 VITAL SIGNS

	0 HR	1HR	2HR	3HR	4HR
Systolic blood pressure (mm Hg)	|____|	|____|	|____|	|____|	|____|
Diastolic blood pressure (mm Hg)	|____|	|____|	|____|	|____|	|____|
Heart rate (per minute)	|____|	|____|	|____|	|____|	|____|

If patient experiences thoracic pain, immediately perform an EKG and administer nitro-compound. Inform Roussel Laboratories at once.

CRF # |0214| Center |__|__|__|__|__| 5 Subject |__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (Day 3)

4.2 - PAINFUL CONTRACTIONS OF UTERUS No___ Yes___

If YES, severity: |___|

1=mild
2=moderate
3=severe, no treatment required
4=severe, requiring treatment

If treatment(s) required, specify:

NAME	DOSE	ROUTE
_____ |___| _____ |___| _____ |___|
_____ |___| _____ |___| _____ |___|
_____ |___| _____ |___| _____ |___|

PREMEDICATION TAKEN No___ Yes__
(Not-automatic, is left up to discretion of investigator before administering Misoprostol)

If YES, specify:

NAME	DOSE	ROUTE
_____ |___| _____ |___| _____ |___|
_____ |___| _____ |___| _____ |___|
_____ |___| _____ |___| _____ |___|

Roussel Laboratories
STUDY : FFR/91/486/14
Product: RU38486

CRF # |0215| 1 Center |__|__|__|__| 5 Subject |__|__|__|__| 10

ADMINISTRATION OF MISOPROSTOL (Day 3)

[redacted]

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

[redacted]

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

[redacted]

CRF # |0204| | Center |__|__|__| | Subject |__|__|__|__|10

ADMINISTRATION OF MISOPROSTOL (D3)

4.3 - NAUSEA AND VOMITING

NAUSEA No___ Yes___

If YES, severity |__|

1=mild
2=moderate
3=severe, no treatment required
4=severe, treatment required

VOMITING No___ Yes___

If YES, severity |__|

1=mild
2=moderate
3=severe, no treatment required
4=severe, treatment required

If treatment for nausea or vomiting was required, specify:

NAME	DOSE	ROUTE
_____	_____(8)	_____
|_____|		|__|
_____	_____(8)	_____
|_____|		|__|

[redacted]

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).

One page for each clinical or biological occurrence.

[redacted]

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).

One page for each clinical or biological occurrence.

[redacted]

(Not including uterine contractions, nausea, vomiting, diarrhea

Roussel Laboratories
STUDY : FFR/91/486/14
Product: RU38486

CRF # |0217| Center |__|__|__|__|5 Subject |__|__|__|__|10

FOLLOW UP VISIT (D8 - D15)

DATE of the VISIT |___|/|___|/|___|
dd / mm / yy

1 - RESULT OF TREATMENT |___|

1=termination of pregnancy, complete expulsion
2=termination of pregnancy, ovule or placenta retained
3=ongoing pregnancy
4=surgical procedure for hemostatic indication (to stop bleeding)

IN CASE PREGNANCY IS TERMINATED AND EXPULSION COMPLETED:

Date of ovular expulsion |___|/|___|/|___| Time |___|:|___|
dd / mm / yy hr : mn

IF EXPULSION DID NOT OCCUR, ONGOING PREGNANCY OR SURGICAL PROCEDURE FOR HEMOSTATIC INDICATION:

Date of surgical procedure |___|/|___|/|___|
dd / mm / yy

Nature: |___|

1=endo-uterine aspiration
2=uterine revision
3=other, specify _____

[redacted]

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

CRF # |0217| Center |__|__|__|__|__| Subject |__|__|__|__| 10

FOLLOW-UP VISIT (Day 8 - Day 15)

2 - TOLERANCE

2.1 - UTERINE BLEEDING No___ Yes___

If YES:

DATE bleeding STARTED |___|/|___|/|___|
dd / mm / yy

TOTAL DURATION of bleeding (in days) |___|

DUE TO BLEEDING IS IT NECESSARY:

- to test concentration of hemoglobin No___ Yes___

If YES, date of test please include |___|/|___|/|___|

Value (g/dl) |___|.|__|

- a transfusion if yes, include No___ Yes___

If YES, number of units of packed red cells |____|

- medical treatment No___ Yes___

If YES, what kind _____

2.2 - ANY ADVERSE EVENT OTHER THAN UTERINE CONTRACTIONS, NAUSEA, VOMITING OR DIARRHEA DURING THE 4 HOURS FOLLOWING MISOPROSTOL No___ Yes___

If YES, ~~report~~ symptoms on page 14.

3. STARTED TAKING ORAL CONTRACEPTIVE BEFORE THIS FOLLOW-UP VISIT No___ Yes___

If YES - Date Started |__|/|__|/|__|

Name of the product _____
|____|

[redacted]

(Not including uterine contractions, nausea, vomiting, diarrhea
during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

[redacted]

(Not including uterine contractions, nausea, vomiting, diarrhea
during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

NATURE OF THE SYMPTOM_____

START DATE |___|/|___|/|___| Time |___|:|___|
dd / mm / yy hh mn

STOP DATE |___|/|___|/|___| Time |___|:|___|
dd / mm / yy hh mn

SEVERITY 1=mild, 2=moderate, 3=severe |__|

RELATED TO THE MIFEPRISTONE TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

RELATED TO THE MISOPROSTOL TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

ACTION REQUIRED? No___ Yes___

If YES, specify_____

Roussel Laboratories
STUDY : FFR/91/486/14
Product: RU38486

CRF # |0207| Center |__|__|__|__|__| Subject |__|__|__|__|

ADVERSE EVENTS - SYMPTOMS

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

NATURE OF THE SYMPTOM_____

START DATE |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hh mn

STOP DATE |__|__|/|__|__|/|__|__| dd / mm / yy Time |__|__|:|__|__| hh mn

SEVERITY 1=mild, 2=moderate, 3=severe |__|

RELATED TO THE MIFEPRISTONE TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

RELATED TO THE MISOPROSTOL TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

ACTION REQUIRED? No___ Yes___

If YES, specify_____
_____

OUTCOME OF EXPERIENCE

|__| Recovered
|__| Side-effects, specify_____
|__| Died
Date (dd/mm/yy) |__|__|/|__|__|/|__|__|

Could be related to treatment No___ Yes___

COMMENTS_____
_____

In case of a serious adverse event, the investigator should immediately contact the authorities at Roussel Laboratories by telephone.

Roussel Laboratories
STUDY : FFR/91/486/14
Product: RU38486

CRF # |0207| Center |__|__|__| Subject |__|__|__|__|

ADVERSE EVENTS - SYMPTOMS

(Not including uterine contractions, nausea, vomiting, diarrhea during the 4 hours following the intake of Misoprostol).
One page for each clinical or biological occurrence.

NATURE OF THE SYMPTOM_____

START DATE |__|__|/|__|__|/|__|__| Time |__|__|:|__|__|
dd / mm / yy hh mn

STOP DATE |__|__|/|__|__|/|__|__| Time |__|__|:|__|__|
dd / mm / yy hh mn

SEVERITY 1=mild, 2=moderate, 3=severe |__|

RELATED TO THE MIFEPRISTONE TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

RELATED TO THE MISOPROSTOL TREATMENT |__|
0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable

ACTION REQUIRED No___ Yes___

If YES, specify_____
_____

OUTCOME OF EXPERIENCE

|__| Recovered
|__| Side-effects, specify_____
|__| Died
~~Date~~ (dd/mm/yy) |__|__|/|__|__|/|__|__|

Could be related to treatment No___ Yes___

COMMENTS_____
_____

In case of a serious adverse event, the investigator should immediately contact the authorities at Roussel Laboratories by telephone.

Roussel Laboratories
STUDY : FFR/91/486/14
Product: RU38486

CRF # |0218| Center |__|__|__|__|5 Subject |__|__|__|__|10

HEMOGLOBIN RATE

	D 1 (before taking Mifepristone)	D8 - D15 Follow up visit
DATE taken (dd/mm/yy)	|__|/|__|/|__|	|__|/|__|/|__|
HEMOGLOBIN (g/dl)	|__|:|__|	|__|:|__|

CONCLUSION

Are there any DEVIATIONS FROM THE PROTOCOL? No___ Yes___

If YES, specify _____
_____
_____
|__|

REASONS for deviation:

ANY OTHER COMMENTS:

NAME of Investigator

SIGNATURE (obligatory)

STAMP (obligatory)