5. Audit of French Clinics

a. A 100% audit of 16 French study sites to confirm completeness of information from source documents to electronic database is currently being conducted.

b. Audit is to be completed by the end of 1995.

APPEARS THIS WAY
ON ORIGINAL

6. Strategy and Timing of Submission of Additional Information to NDA

a. Analysis and Report of Results from US Clinical Trials

i. Submission of the four-month Safety Update which will include

- Safety data from US Studies A and B
- Adverse events received from any source since NDA filing
- Additional study reports (nonclinical and clinical) received from Roussel Uclaf since NDA filing

ii. Submission of a supplement to the approved NDA which will include

- Full study report of US Study A (Efficacy and safety results)
- Full study report of US Study B (Efficacy and safety results)
- Report on integration of efficacy and safety data from US Studies A and B
- Integrated summary of efficacy results from two French pivotal studies and US Studies A and B
- Integrated summary of safety results from two French pivotal studies and US Studies A and B
- Revised labeling as appropriate based on above information

6. Strategy and Timing of Submission of Additional Information to NDA (Cont.)

b. Information on New Manufacturers

i. Submission of Drug Master Files by the new manufacturers of the drug substance and drug product

ii. Submission of supplement(s) to the approved NDA which will reference the Drug Master Files and request approval of the new manufacturers.

APPEARS THIS WAY
ON ORIGINAL

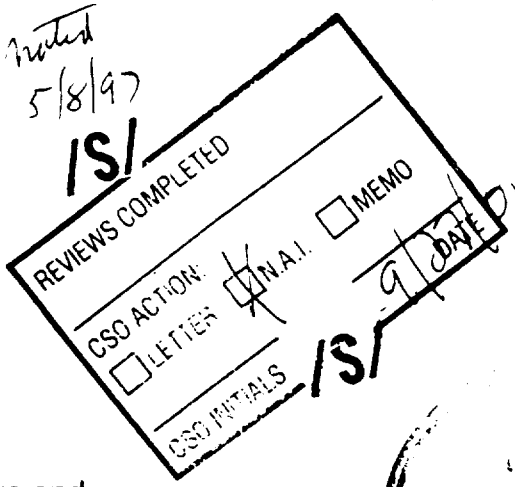
The Population Council

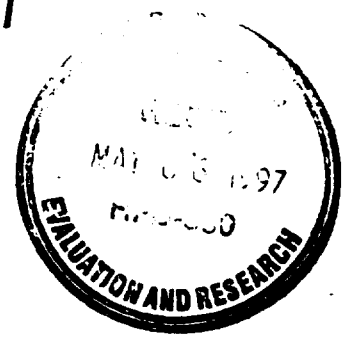
ıter for
medical Research

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

ORIGINAL
IM 185

Faxed 5/8/97





May 5, 1997

VIA FED EX

———

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

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 185
Information Amendment - Clinical: Results from the U.S. Clinical Trial on "Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days."

Dear ———

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

Enclosed please find the results on the clinical trials entitled "Evaluation of the efficacy, safety and acceptability of mifepristone and misoprostol in inducing abortion in pregnant women with amenorrhea of up to 63 days." These trials were conducted under identical protocols (166A and 166B) that were conducted concurrently in the United States to evaluate the regimen of 600 mg mifepristone followed by an oral dose of 400μg misoprostol two days later. The results from these studies are presented in the following series of reports. An overall summary of the combined results on safety and efficacy from both Protocols 166A and B is presented in Appendix 1 of this letter. This report also contains a comparison of the U.S. safety and efficacy results to those of the French studies presented in the Council's NDA 20,687 on mifepristone. An overall summary of the combined results on acceptability and feasibility from both protocols 166A and B are presented in Appendix 2 of this letter. These results on efficacy, safety, acceptability and feasibility will be presented publicly for the first time by the Population Council on May 15,

1997 in New York City. This will occur at a meeting on Medical Abortion co-sponsored by the New York Academy of Medicine and Planned Parenthood of New York City.

In addition, we are including the draft versions of the individual study reports for results of Protocol 166A and results of Protocol 166B, which will be submitted in their final form to NDA 20,687 later this year. At this time, we provide for your review, the text of the study report and the main summary tables for each study report. We also have included the list of appendices that will accompany each study report. Although the actual contents of the appendices are not included here, they will be submitted to the NDA 20,687.

These study reports, of Protocol 166A and 166B are organized as follows: Study Report 166A of safety and efficacy results is contained in Volume 1. Study Report 166B of safety and efficacy results is contained in Volume 2. The Study Reports of acceptability and feasibility results for Protocol 166A and Protocol 166B are contained in Volume 3.

Please be aware that these Study Reports are in draft form and are being submitted at this time to provide you with more detailed information than is in the summary of combined results. The draft Study Reports also have an earlier cut off data than does the summary report.

Please feel free to contact me if you have any questions on the enclosed information.

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

AR:yho

Attachments to this letter:
FDA Form #1571
Appendix 1 - Summary of the combined results on safety and efficacy from Protocols 166A and B.
Appendix 2 - Summary of the combined results on acceptability and feasibility from Protocol 166A and B.

Enclosures:
Volume 1 - Study Report 166A : safety and efficacy results
Volume 2 - Study Report 166B : safety and efficacy results
Volume 3 - Study Report 166A : acceptability and feasibility results
- Study Report 166B : acceptability and feasibility results

APPENDIX 1

APPEARS THIS WAY
ON ORIGINAL

RESULTS FROM

POPULATION COUNCIL

PROTOCOLS 166A AND 166B

INTEGRATED SUMMARY

Evaluation of the Efficacy and Safety of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up To 63 Days

These studies were sponsored by: The Population Council, Inc.
New York, NY

The following investigators and centers participated:

Principal Investigators - Study 166A

Principal Investigator	Center No.	Center Location
Dr. Daniel R. Mishell, Jr.	1	University of Southern California - Women's and Children's Hospital 1240 N. Mission Road, Room 2K1 Los Angeles, CA 90033
Dr. Susan Haskell	2	Planned Parenthood of Greater Iowa 851 19th Street Des Moines, IA 50314
Dr. Suzanne T. Poppema	3	Aurora Medical Services, Inc. 1207 N. 200th Street, Suite 214 Seattle, WA 98133
Dr. Judy Tyson	4	Planned Parenthood of Northern New England 23 Mansfield Avenue Burlington, VT 05401
Dr. Paul Blumenthal	5	Johns Hopkins Bayview Medical Center Department of OB/Gyn 4940 Eastern Avenue Baltimore, MD 21224
Dr. Lynn Borgatta	6	Planned Parenthood of Westchester and Rockland 175 Tarrytown Road White Plains, NY 10607-1616
Dr. Tyrone C. Malloy	7	Feminist Women's Health Center 580 Fourteenth St., NW Atlanta, GA 30318
Dr. Eugene Rothenberg	8	Planned Parenthood of Central New Jersey 69 East Newman Springs Road Shrewsbury, New Jersey 07702

Principal Investigators - Study 166B

Principal Investigator	Center No.	Center Location
Dr. Alfred N. Poindexter	21	Planned Parenthood of Houston & S.E. Texas, Inc. 3601 Fannin Houston, Texas 77004
Dr. Peter Vargas	22	Planned Parenthood of the Rocky Mountains 1537 Alton Street Aurora, CO 80010
[redacted]	[redacted]	[redacted]
Dr. Carolyn Westhoff	24	Columbia University College of Physicians and Surgeons 630 W. 168th Street New York, NY 10032
Dr. Mark Nichols	25	Oregon Health Sciences University Department of OB/GYN, L466 3181 SW Sam Jackson Park Road Portland, OR 87201-3098
Dr. Katherine L. Sheehan	26	Planned Parenthood of San Diego & Riverside Counties 1075 Camino Del Rio South San Diego, CA 92108
Dr. Catherine L. Dean	27	Washington University School of Medicine 1150 Graham Road St. Louis, MO 63031
Dr. Mitchell D. Creinin	28	Magee-Women's Hospital Dept. of OB/GYN 300 Halket Street Pittsburgh, PA 15213-3180
Dr. Laszlo Sogor	29	PRETERM 12000 Shaker Blvd. Cleveland, OH 44120

Patient Enrollment Dates:

Protocol 166 A	September 13, 1994	to	August 23, 1995
Protocol 166 B	November 10, 1994	to	September 12, 1995
Integrated Study	**September 13, 1994**	**to**	**September 12, 1995**

APPEARS THIS WAY
ON ORIGINAL

Both Studies were conducted in compliance under Good Clinical Practice guidelines.

APPEARS THIS WAY
ON ORIGINAL

Cut-off date for Report: **May 5, 1997**

Any differences between the results presented in this integrated report and in the individual study reports for Protocols 166A and 166B (in volumes 1 and 2 respectively of this submission) are due to modifications made in the database and further analysis subsequent to the writing of the individual reports, which had a cut-off date of April 25, 1997.

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ON ORIGINAL

CONTENTS

APPENDIX C
THE POPULATION COUNCIL PROTOCOL 166A
STUDY PROTOCOL AND AMENDMENTS AND GENERAL INFORMATION

A. Date Protocol Filed to IND —— and Dates Amended:

Date Filed: August 3, 1994
Dates Amended: November 2, 1994
April 27, 1995
May 2, 1995

B. Protocol Cover Sheet

C. Protocol, Protocol Amendments, Sample Informed Consent Form, and Case Report Forms

D. Mifepristone and Misoprostol Drug Lot Numbers

Mifepristone: JMP25524-109 (all centers)
Misoprostol:
Center 1: 4H441, 3P414, 3S422, 4H439, 4N452
Center 2: 04F434, 04N454, 04S462, 05B468
Center 3: 4H440, 4N451, 4S459, 4H441
Center 4: 4H438A, 4B425, 4S462
Center 5: 4B425, 4S462, 4P468
Center 6: 5A465, 4N451
Center 7: 4K446
Center 8: 5A464, 4S461

E. Publications Based on the Study

None

APPEARS THIS WAY
ON ORIGINAL

APPENDIX C
THE POPULATION COUNCIL PROTOCOL 166A
PROTOCOL COVER SHEET

Study Phase: III

Name of Drug:
Active Ingredient: Mifepristone
Dosage: 600 mg
Route of Administration: oral
Duration of Treatment: single dose

Objective: The study was conducted to evaluate the effectiveness, safety, acceptability, feasibility of using mifepristone and misoprostol, in a setting within the United States health care system, for the induction of abortion in women whose duration of amenorrhea was no more than 63 days.

Patient Population: women at least 18 years of age who were ≤ 63 days from onset of their last menstrual period and who requested a voluntary termination of pregnancy.

Structure: open-label, single treatment group with patients stratified by duration of amenorrhea (≤ 49, 50 - 56, 57 - 63 days).
Multicenter: yes
Number of Centers: 8
Common Training: yes
Blinding: none
Method of Patient Assignment: all patients were assigned to treatment with 600 mg mifepristone and 400 µg misoprostol.

Concurrent Control: none

Estimated Total Sample Size: 1050

Statistical Rationale Provided: no

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

Adverse Reactions: observed/volunteered

Plan for Data Analysis: yes

Telecon Meeting Minutes

Date: October 14, 1997 **Time**: 1:00 PM - 1:15 PM **Location**: 17B-43

IND [redacted] **Drug Name**: mifepristone tablets

External Participant: The Population Council

Type of Meeting: regulatory guidance

Meeting Chair: [redacted]

External Participant Lead: Beverly Winikoff, M.D.

Meeting Recorder: [redacted]

FDA Attendees:

[redacted] Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

[redacted] DNDCII @ DRUDP (HFD-580)

[redacted] Consumer Safety Officer, DRUDP (HFD-580)

External Constituents:
Beverly Winikoff, M.D., Director of Reproductive Health

Meeting Objectives:
to provide guidance regarding retesting of expired tablets prior to release for clinical trial

Discussion Points:

- Sponsor issues
  - the sponsor currently has approximately [redacted] tablets which expired in July of this year
  - these tablets are from the same drug lots used in the U.S. clinical trials
  - the sponsor would like to use these tablets in early termination of pregnancy studies outside of the United States
  - guidance is requested regarding what type of testing would be required to extend the expiration date of these tablets
  - the sponsor proposes utilizing the testing facility which initially assayed the tablets in the U.S.
  - the testing facility has all of the requisite testing specifications to appropriately assay the expired tablets

Decisions Reached:

- the proposed testing of the expired tablets is appropriate
- the sponsor must submit the assay results to the IND once they are available
- if the tablets pass the specifications, the expiration date may be extended for six months, if there are further tablets left at the end of those six months, the tablets must be retested, if the tablets pass, they again may have a six month extension of the expiration date
- any tablets that do not pass the specifications may not be utilized

Unresolved Issues: none

Action Items: see decisions reached

/S/ 10/15/97
Minutes Preparer

/S/ 10/15/97
Concurrence, Chair

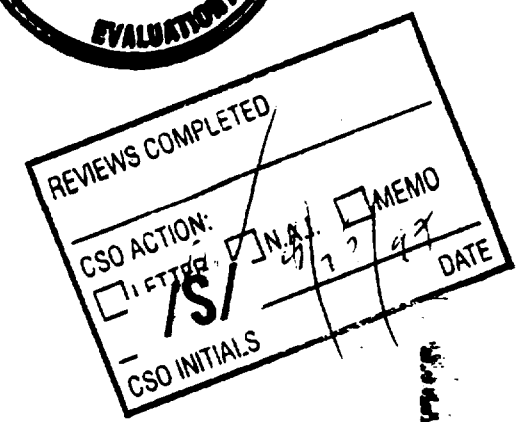
cc:
Orig. IND
HFD-580
HFD-580/ —
HFD-580 —
HFD-580 — 10.14.97. —
concurrences: — 10.14.97. — 10.14.97

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Population Council

ORIGINAL



August 20, 1997

VIA FED EX

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

Subject: IND ——— Mifepristone Tablets, 200 mg
Submission Serial Number: 190
Protocol Amendment: New Investigator/Change Status of Subinvestigator to Co-principal Investigator

Dear ———

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

With this submission, we wish to amend our IND to change the status of a subinvestigator to a co-principal investigator in the clinical investigation of mifepristone conducted under Protocol 166B.

In accordance with Submission Serial Number 111, dated December 22, 1994, the above IND was amended to include Dr. Mark D. Nichols as an investigator in the mifepristone trial. In that submission, the enclosed Statement of Investigator Form (Form FDA 1572) signed by Dr. Nichols listed as one of the subinvestigators who would be participating in the study. Because has played a substantial role in the conduct of this clinical trial, we wish to amend our IND to include both Drs. Nichols and as co-principal investigators at this particular clinic site. Attached is a copy of a modified and new Statement of Investigator Form for Drs. Nichols and respectively. Also, included is a copy of s current curriculum vitae. Dr. Nichols' curriculum vitae was included in Submission 111.

Verbal
8/25/97
/S/

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

Population Council

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

Sincerely yours,

Ann Robbins

Ann Robbins, Ph.D.
Scientist

AR:yaho

APPEARS THIS WAY
ON ORIGINAL

Population Council

ORIGINAL
YY 192

12/4/97
/S/

December 1, 1997

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

Subject: IND — Mifepristone Tablets, 200 mg
Submission Serial Number: 192
Annual Report

Dear ———

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

Enclosed please find our Annual Report which describes recent activities in the development program with mifepristone. The cut-off date for this report is July 31, 1997 and the document covers the period of time since July 31, 1996 cut-off date for our last annual report (Submission 170) which was submitted on September 30, 1996.

In the time period covered by this report, various informational amendments (Amendment Nos. 003 through 007) and correspondence were submitted to our pending NDA 20-687 which also provides for the use of mifepristone in the induction of abortion. We ask that these NDA submissions be incorporated by reference in this IND.

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

Sincerely yours,

Frederick H. Schmidt

Frederick H. Schmidt, Ph.D.
Scientist

Enclosure

lm

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO [illegible] /S/ DATE

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

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

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

Summary information on safety experience in Protocols 166A and 166B was previously submitted in the 1996 Annual Report (Submission Serial Number 170 - September 30, 1996) to this IND and in the draft preliminary report on the studies included in Submission Serial Number 185 (May 5, 1997). Final analysis and report preparation for the studies are now underway and no additional information on the studies is available at this time.

During the period covered by this Annual Report, four summary reports on the accumulating safety experience with mifepristone have been received from the French manufacturer of the product. These documents, as listed below, summarize the worldwide experience with mifepristone in both approved and investigational indications which was received by the manufacturer during the time periods covered by the individual reports. Copies of the reports are included in this section.

Periodic Safety Update Report No. 6 (from December 1, 1996 to May 31, 1997)
Periodic Safety Update Report No. 5 (from June 1, 1996 to November 30, 1996)
Periodic Safety Update Report No. 4 (from December 1, 1995 to May 31, 1996)
Quarterly Safety Line Listing (from July 1, 1996 to September 30, 1996)

APPEARS THIS WAY
ON ORIGINAL

Population Council

noted 6/21/00 /S/

ORIGINAL

6/21/00 /S/

11209-S2

June 19, 2000

By Federal Express

CENTER FOR DRUG EVALUATION AND RESEARCH RECD JUN 20 2000 HFD-580

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

/S/ 6/21

CSO INITIALS DATE

Subject: IND ——— Mifepristone Oral Tablets, 200 mg
Submission Serial Number: 209
IND Safety Report – Initial Written Report

Dear ———

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

The copy of the notification by the principal investigator to her IRB regarding this serious adverse event is attached along with our completed MedWatch form (FDA Form 3500A). In the notification to the IRB, the principal investigator states that "This patient's condition is probably unrelated to the study treatment".

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

Sincerely yours,

Frederick H. Schmidt

Frederick H. Schmidt, Ph.D.
Scientist

Center for Biomedical Research
1230 York Avenue, New York, New York 10021
Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org http://www.popcouncil.org

Enc.

cc: Sandra P. Arnold, Population Council

Medical Director, Exelgyn

APPEARS THIS WAY
ON ORIGINAL

Population Council

Sandra P. Arnold
Vice President
Corporate Affairs

ORIGINAL

YX
207

noted
5/10/00
/S/

May 5, 2000

VIA FEDERAL EXPRESS

not /S/ 5/26/00

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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.L ☐ MEMO
/S/ 5/30/00
CSO INITIALS DATE

/S/ 5/30/00

Subject: IND —— - Mifepristone Oral Tablets, 200 mg
Submission Serial Number: 207
Annual Report

Dear ——————

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

Please find enclosed our Annual Report, which provides information on activities in the development program with mifepristone. The cut-off date for this report is February 29, 2000, and the document covers the period of time since the July 31, 1997 cut-off date for our last Annual Report (Submission Serial Number 192) which was submitted on December 1, 1997.

In the time period covered by this report, amendments regarding various issues such as proposed product labeling; new chemistry, manufacturing and controls information; Safety Update Reports; and reports of clinical studies have been submitted to our pending NDA 20-687 which also provides for the use of mifepristone in the induction of abortion. We ask that these NDA submissions be incorporated by reference in this IND.

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

Very truly yours,

Sandra Arnold

Enclosures

cc:

One Dag Hammarskjold Plaza, New York, New York 10017
Telephone: (212) 339-0663 Facsimile: (212) 980-3710 Email: sarnold@popcouncil.org http://www.popcouncil.org

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

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

As mentioned above, a combined summary of the safety experience observed in the two clinical studies completed in this country under Protocols 166A and 166B has been previously submitted to NDA 20-687 (Amendment 024 - June 3, 1999). As concluded in that summary, the combined regimen of mifepristone and misoprostol was regarded as a safe method of medical abortion for gestational ages of up to 63 days. In the studies, an increase in the incidence of some adverse effects (abdominal pain, headache, diarrhea, nausea, vomiting and uterine hemorrhage) was noted in the 50-56 and 57-63 gestational age groups as compared to the ≤ 49 days group. There were no deaths and no patients were discontinued due to an adverse event.

The treatment procedure with mifepristone and misoprostol is designed to induce vaginal bleeding and uterine cramping necessary to produce an abortion. Therefore, nearly all women who receive the two products will report adverse reactions. **Attachment C**, taken from the combined summary of safety for the two studies, lists the rates of adverse reactions which occurred in at least 1% of the patients in Protocols 166A and 166B.

Additionally, during the period covered by this Annual Report, three Periodic Safety Update Reports, as listed below, were received from the French manufacturer of mifepristone. These documents summarize the worldwide experience with mifepristone in both approved and investigational indications which was received by the French manufacturer during the time periods covered by the individual documents. Copies of Periodic Safety Update Reports Nos. 7 and 8 are available in the second Safety Update Report to NDA 20-687 which was submitted on August 3, 1999 (Amendment 031) and a copy of Periodic Safety Update Report No. 9 is available in Safety Update Report # 3 which was submitted to NDA 20-687 on March 30, 2000 (Amendment 043).

Periodic Safety Update Report No. 7 (from 06/01/97 to 11/30/97)
Periodic Safety Update Report No. 8 (from 12/01/97 to 08/31/98)
Periodic Safety Update Report No. 9 (from 09/1/98 to 11/30/99)

ATTACHMENT C

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ON ORIGINAL

Rates of Adverse Reactions in Protocols 166A and 166 B

(Reactions which occurred in ≥1% of patients)

Adverse Event	
Abdominal pain *(others than stomach & intestinal)*	97%
Nausea	67%
Vomiting	34%
Headache	32%
Diarrhea	23%
Dizziness	12%
Back pain	9%
Fatigue	9%
Uterine hemorrhage	7%
Fever	4%
Viral infection	4%
Vaginitis	4%
Dyspepsia	3%
Rigors	3%
Anemia	2%
Anxiety	2%
Asthenia	2%
Insomnia	2%
Leg Pain	2%
Leukorrhea	2%
Sinusitis	2%
Syncope	2%
Abdominal pain *(stomach and intestinal)*	1%
Allergy	1%
Constipation	1%
Depression	1%
Flatulence	1%
Malaise	1%
Pain	1%
Pharyngitis	1%
Increased sweating	1%

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

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

The following individual safety reports were received by the sponsor and submitted to this IND during the period covered by this report.

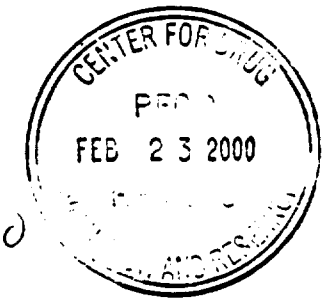
Individual Reports of Adverse Reactions Received by the Population Council and Reported to IND

IND Submission Number – Date	Reference Number	Country	Event
191-11/21/97	S970001GB/MIF1	UK	Fetal Malformation
193-04/14/98	S980006GB/MIF1	UK	Disseminated Intravascular Coagulation
198-12/17/98	S980017GB/MIF1	UK	Fetal Malformation
200-02/18/99	S990001F/MIF1	France	Urticaria Generalized
201-02/26/99	S980017GB/MIF1 (Follow-Up)	UK	Follow-up report from embryologist that association with drug is not possible
203-11/23/99	M99001	Tunisia	Allergic Reaction
204-12/16/99	M99002 M99003	India	Heavy Bleeding (2 Patients)
205-02/03/00	T20000003US/MIF1	US	Carcinoma of Omentum
206-02/22/00	S20000003F/MIF1	France	Hemiplegia, Cerebrovascular Attack, Cephalgia

Population Council

February 22, 2000

mailed 2/25/00 /S/



By FedEx

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

/S/ 2/25/00

/S/ 4/5/00

ORIGINAL

N-206-52

Subject: IND — Mifepristone Tablets, 200 mg
Submission Serial Number: 206
IND Safety Report-Initial Written Report

Dear ———

Enclosed please find an initial report of a serious adverse reaction that has been received by the Population Council from Exelgyn Laboratories (Paris, France). The event was brought to the attention of Exelgyn by the French Health Agency.

[

The summary of the available information is presented on the attached form prepared by Exelgyn.

]

Exelgyn indicated that this adverse event was classified as not related to mifepristone and they have requested further information on this case. We will submit a follow-up report as soon as any additional information is available.

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

Sincerely yours,

Frederick H. Schmidt

Frederick H. Schmidt, Ph.D.
Scientist

cc: S. Arnold
E. Johansson
——— The Danco Group
I. Spitz

FHS: lm

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS /S/ 4/ DATE

Telephone: (212) 327-8731 Facsimile: (212) 327-7678 Email: cbr@popcouncil.org
Center for Biomedical Research
1230 York Avenue, New York, New York 10021
http://www.popcouncil.org

IND [redacted]

AUG [illegible]

The Population Council
Center for Biomedical Research
Attention: Irving M. Spitz, M.D.
Coordinator, Clinical Research
1230 York Avenue
New York, NY 10021

Dear Dr. Spitz:

Reference is made to your Notice of Claimed Investigational Exemption for a New Drug (IND) for RU 38486.

We also refer to your amendments of February 27 and April 24, 1985, and to our letter of April 5, 1985.

We have completed our review of your latest submission and conclude that it is appropriate to expand the studies to include more subjects at the 100 mg and 50 mg daily dosages X 7 days.

Your cooperation is appreciated.

Sincerely yours,

/S/

[redacted]

Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: Orig IND
HFN-810
HFN-810, [redacted] 8/7/85
HFN-810 [redacted] /7-22-85/0236R
rch/7/31/85
R/D init. by [redacted] 7/22/85
Concurrence: [redacted] /7/29/85

GENERAL CORRESPONDENCE

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Telephone (212) 570-8731
Telex: 238274 POBI UR

IND AMENDMENT

BEST POSSIBLE COPY

April 24, 1985

~~Progress Report~~ Correspondence

[redacted]

Division of Metabolism and Endocrine
Drug Products/HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics
Food and Drug Administration
Rockville, Maryland 20857

Re: IND ——— RU486

Dear ———

The following represents the current status of our studies in abortion. In Los Angeles five subjects received 400 mg per day for four days and did not abort. Four subjects received 200 mg per day for four days and one aborted. In these studies subjects complained of nausea and vomiting, especially with the higher dose.

Of the 28 subjects treated with the regimen of 100 mg per day for seven days in Uppsala there were twenty complete abortions, five incomplete abortions, and three failures. There were no untoward effects. In Los Angeles 33 subjects have now had the same regimen of 100 mg per day for seven days and there have been 28 complete abortions.

In Paris, a decremental dose schedule of 400, 300, 200, and 100 mg per day was given for four days and showed abortion in only six of ten subjects. With this dose there was also nausea and vomiting. Using the regimen of 100 mg per day for seven days, there were abortions in eight of ten subjects.

Studies in post-menopausal women have showed that RU486 has some progesterone agonistic activity. I think that with the higher doses there is ~~an~~ agonistic effect and this is why the results are not so good. Furthermore, it is also possible that there is some antiglucocorticoid effect with the higher doses. There were no changes in cortisol with the regimen of 100 mg per day for seven days. On the other hand, with the higher doses used in Paris and Los Angeles there were transient increases in cortisol which decreased to the normal range following cessation of therapy.

It has been our preliminary conclusion that the regimen of RU486 of 100 mg per day for seven days is without any untoward effects.

We also want to do a statistical analysis on the effect of duration of pregnancy and evaluate if hormonal or other factors can predict the outcome. These are the reasons why we wish to enroll a larger number of subjects. In Uppsala we have recently started giving RU486 in doses of 50 mg per day for seven days. To date, of the ten subjects who have been treated there have been seven complete abortions.

I trust that this answers your queries. I am currently preparing a full documentation of all clinical effects, as well as biochemical parameters in these various studies and this will be forwarded to your office shortly.

Yours very sincerely,

Irving M. Spitz, M.D.
Coordinator, Clinical Research

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Telephone (212) 570-8731
Telex: 238274 POBI UR

IND AMENDMENT
CB

March 12, 1985

Food and Drug Administration
Division of Metabolism
and Endocrine Drug Products
National Center for Drugs and Biologies
Food and Drug Administration
HFN 130
5600 Fishers Lane
Rockville, Maryland 20857

Re: IND for RU486 (IND No. [redacted]
Administration of RU486 and hCG in the luteal phase

Dear [redacted]

Enclosed please find our report on the above project.

With my best wishes.

Sincerely yours,

Irving M. Spitz, M.D.
Coordinator
Clinical Research

IMS/rh

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☑ N.A.I.

CSO INITIALS [redacted] 4.23.85
DATE

See ltr dtd 4.15.85
re: A of 12.7.84

RECEIVED
HFN-810
MAR 18 1985
CENTER FOR DRUGS
AND BIOLOGICS

MIF 004931

Protocol 31

THE RESPONSE TO RU 486 WHEN ADMINISTERED TOGETHER WITH hCG IN THE LUTEAL PHASE IN NORMAL WOMEN

1. INTRODUCTION

In the absence of fertilization, there is a progressive decrease in circulating progesterone levels towards the end of the luteal phase which leads to endometrial bleeding. If implantation occurs however, human chorionic gonadotropin (hCG) from the developing trophoblast stimulates progesterone secretion from the corpus luteum. The administration of exogenous hCG to normal women during the luteal phase simulates early pregnancy. This model has been used to study the action of drugs that interfere with progesterone synthesis, secretion or peripheral action.

RU 486, a synthetic 19-norsteroid derivative, has been shown to have antiprogestational and antiglucocorticoid actions in both man and experimental animals (Philibert, et al., 1981; Herrmann et al., 1982; Philibert et al., 1982a Philibert et al., 1982b; Proulx-Ferland et al., 1982; Gaillard et al., 1984). We reasoned that women with hCG induced prolongation of the luteal phase would be ideal for studying the in vivo action of RU 486. Utilizing this model we have administered hCG in combination with RU 486 in an attempt to demonstrate the antiprogestational activity of the latter. Since RU 486 is also a glucocorticoid antagonist (Philibert et al., 1981; Proulx-Ferland et al., 1982; Gaillard et al., 1984), we also measured serum cortisol. SMA12 and hematology was also assessed to determine if RU 486 had any other untoward effects.

2. MATERIALS AND METHODS

This study was performed on 15 regularly cycling women aged 32 to 40 years of age who had previously undergone surgical sterilization. The nature and aims of the study was explained to all the subjects who then gave their consent. Ten subjects received hCG alone and 18 received hCG combined with various doses of RU 486. In all treatment cycles, the precise day of the LH surge was determined by measuring LH daily in early morning urine samples using Higonavis supplied by [redacted] This day was designated as day 0. On day 9 following the LH surge, daily hCG administration was commenced. Progressively increasing doses (500, 1000, 1500, 3000, 6000, 10,000 and 15,000 IU) were administered each morning from days 9 to 15. In cycles where hCG was combined with RU486, the latter compound was administered on days 12 to 15 inclusive, in a dose of 50, 100, or 200 mg/day. Six subjects received each dose schedule.

In all treatment cycles blood samples were taken each morning, before drug administration from day 9 to day 16, and on alternate days from day 16 to 22 for the measurement of LH, FSH, estradiol, progesterone, and cortisol. These hormones were measured in plasma utilizing the reagents and procedures supplied by the World Health Organization Programme for the Provision of Matched Assay Reagents for the RIA of Hormones in Reproductive Physiology (Hall, 1978). hCG levels were determined using [redacted]

Blood samples for SMA-12 and hematology were taken in each subject prior to treatment, on the last day of hCG administration when it was given alone and on the last day of RU 486 administration in the RU 486-hCG combinations.

3. THE EFFECT OF RU 486 ON MENSTRUAL BLEEDING

None of the women had any complaints during RU 486 administration and there were no alterations in vital signs including pulse rate and blood pressure. When hCG was given alone, bleeding started on days 21 to 24 and the mean duration (± SD) was 5.3 ± 1.8 days. With the hCG-RU 486 combinations, bleeding usually commenced on the second to the fourth day of RU 486 administration and lasted for 2.5 ± 1.4 days. Further bleeding occurred on days 23-28, following the LH surge with the two lower doses and the duration was 2.2 ± 0.8 days. There was no further bleeding with the highest dose of RU 486.

4. THE EFFECT OF RU 486 ON GONADOTROPIN AND SEX STEROID LEVELS IN hCG TREATED WOMEN

During treatment in all cases there was a progressive increase in immunoreactive hCG levels (as measured in the LH assay); the peak was evident on the day following cessation of hCG administration. Thereafter, hCG levels decreased progressively with a half disappearance time of approximately 48 hours. By day 23 following the LH surge, mean values were below 25 mIU/ml which is within the range of basal LH levels seen in the normal luteal phase (Figs 1 & 2). FSH showed a slight but significant increase during treatment with the hCG alone with the hCG-RU 486 combinations. There were, however, no difference in FSH response in the various tests (Figs. 1 & 2).

On day 9 following the LH surge progesterone levels ranged from 12-15 ng/ml in the hCG and hCG-RU 486 cycles. A progressive increase in progesterone levels occurred during hCG administration in all treatment cycles and peak levels ranged from 25-35 ng/ml. There were no differences in progesterone levels in hCG treated or hCG - RU 486 treated cycles. In all

instances progesterone levels gradually decreased to mean levels below 2.5 ng/ml by day 23 following the LH surge (Figs. 1 and 2).

Mean estradiol levels ranged from 140-200 ng/ml during RU 486 treatment and were not different from estradiol levels during treatment.

5. THE EFFECT OF RU 486 ON SERUM CORTISOL

Basal cortisol levels were not different in the hCG treated or hCG-RU 486 combination. There were no changes in cortisol during treatment with hCG alone. In contrast, during the hCG-RU 486 combinations there were significant rises in cortisol levels. The mean peaks were 18.2 ± 3.3, 18.1 ± 2.5, and 24 ± 4.0 ug/100 ml, respectively, with the 50, 100, and 200 mg RU 486 doses. These levels were observed on the last day or the day after completion of RU 486 administration (Fig. 3). These cortisol values were still well within the normal a.m. cortisol range which is 10-25 ug/ml. Cortisol returned to base line after 4 days.

6. SMA-12 RESULTS

a. SGOT (normal range 7-40 mu/ml)

With the highest dose of RU 486 two subjects showed increased values of 57 and 117 mu/ml. In the latter subject an increased value (42 mu/ml) was also noted with the 50 mg dose. A further subject had an elevated level (46 mu/ml) during the control test. These results are shown in Fig. 4.

b. LDH (normal range 100-225 mu/ml)

Three subjects had slightly increased values (231, 252 and 259 mu/ml) in the control study. One subject had an increased value during the hCG test

(247 mu/ml) No changes were apparent during RU 486 administration.

c. Alkaline phosphatase (normal range 30-85 mu/ml)

In one subject there was an increased value (98 mu/ml) in the control study. Decreased values were noted in the control study and during RU 486 and hCG testing in a further subject.

d. Blood urea (normal range 10-20 mg/100 ml)

Analysis of variance showed that blood urea levels decreased with increasing doses of RU 486 (Fig. 5). In no instance was there an increased value.

e. Other Parameters

Isolated abnormal values were seen with albumin, calcium and in inorganic phosphate (Table 1). None of these are believed to be significant. All the remaining biochemical values including bilirubin, total protein, cholesterol, uric acid, sodium, potassium, chloride, CO_2, and glucose were normal. Thus, except for slight changes in SGOT with the highest dose, all other biochemical parameters were in the normal range.

7. Hematology Results

No abnormalities in white count were detected. One subject had a slight increased RBC count in the control study (5.6 million/cm) and also during the highest dose of RU486 (5.2 million/cm).

8. CONCLUSION

This study shows that RU 486 can induce endometrial shedding despite high circulating progesterone and estradiol levels and maintenance of corpus luteum function consequent to exogenous hCG therapy. There were no adverse clinical effects. Hematology was normal. There was a slight rise in SGOT with the highest dose of RU 486 (200 mg/day). The remaining biochemical parameters were normal.

9. REFERENCES

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FIGURES

Figure 1: The effects of hCG on the mean (± SEM) LH, FSH and progesterone levels in 10 women. Increasing doses of hCG were given from days 9 to 15 following the LH surge as indicated in the text. The hCG values are shown on a logarithmic scale. The time and duration of the menstrual bleeding are indicated by the black rectangle.

Figure 2: The effects of hCG and RU 486 on hCG, FSH and progesterone levels in women. hCG was given as indicated in Fig. 1 and RU 486 in a dose of 100 mg per day from days 12 to 15 following the LH surge. The two episodes of menstrual bleeding are indicated by the black rectangles.

Figure 3: The serum cortisol response to hCG alone and the hCG-RU 486 combinations. The duration of treatment was the same as in Fig. 1 and 2.

Figure 4: SGOT responses in individual subjects with the hCG and hCG-RU486 combinations. Each star represents an individual subject. When 2 or more subjects have the same value, the specific number is given.

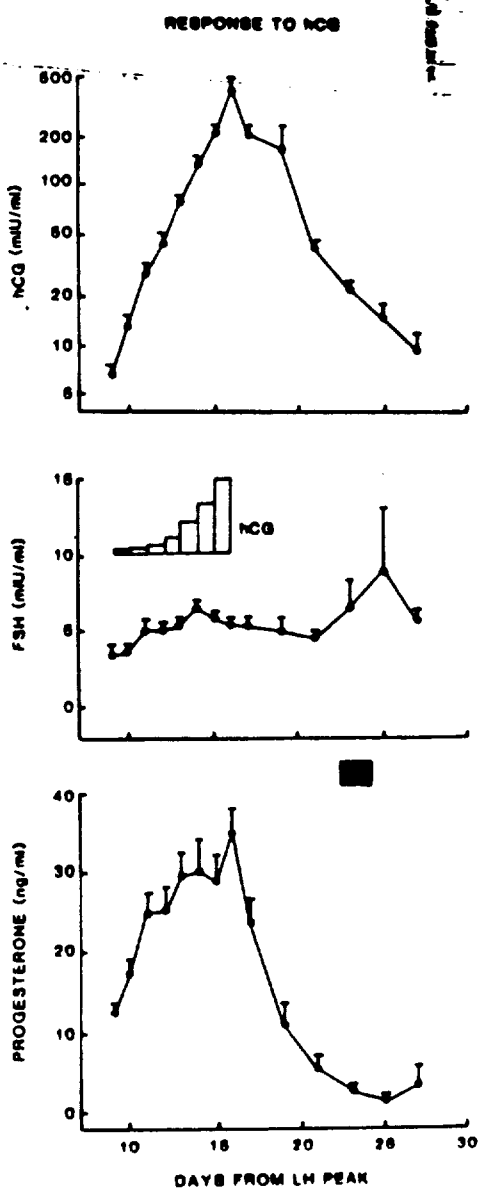
Figure 5: Blood urea responses in individual subjects with the hCG and hCG-RU486 combinations. See legend to Fig. 4.

Table 1

Isolated Abnormal Biochemical Parameters

Parameters	Subject No.	Dose	Value	Normal Range
Albumin	02	hCG alone	5.1	3.5 - 5.0 gm/100 ml
Inorganic phosphate	05	*	2.3	2.5 - 4.5 mg/100 ml
Calcium	05	control	8.4	8.5 - 10.5 mg/100 ml
	07	**	8.2	

* RU486 - 200 mg/day
** RU486 - 50 mg/day



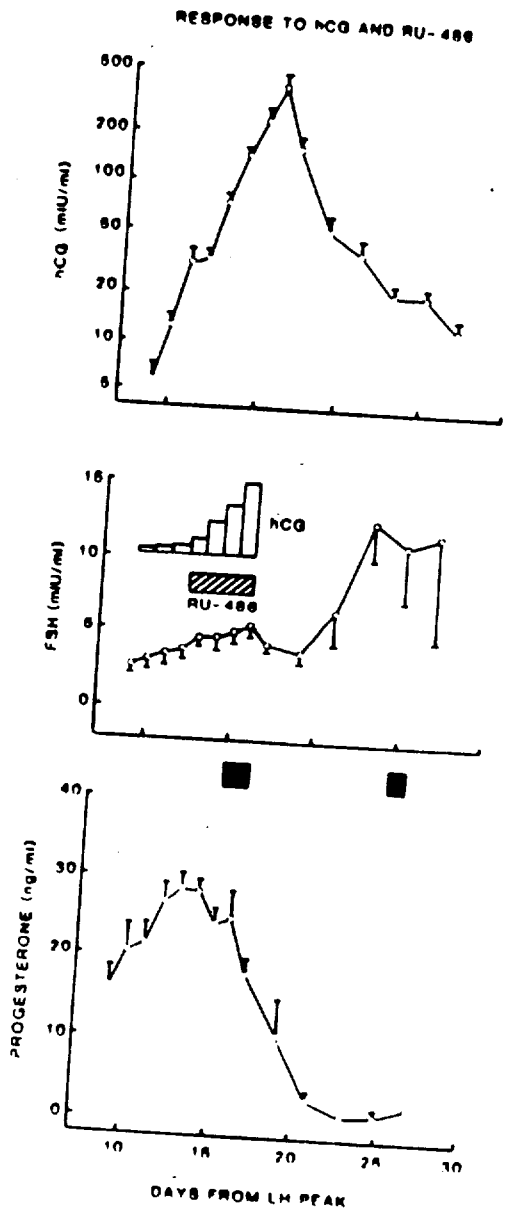
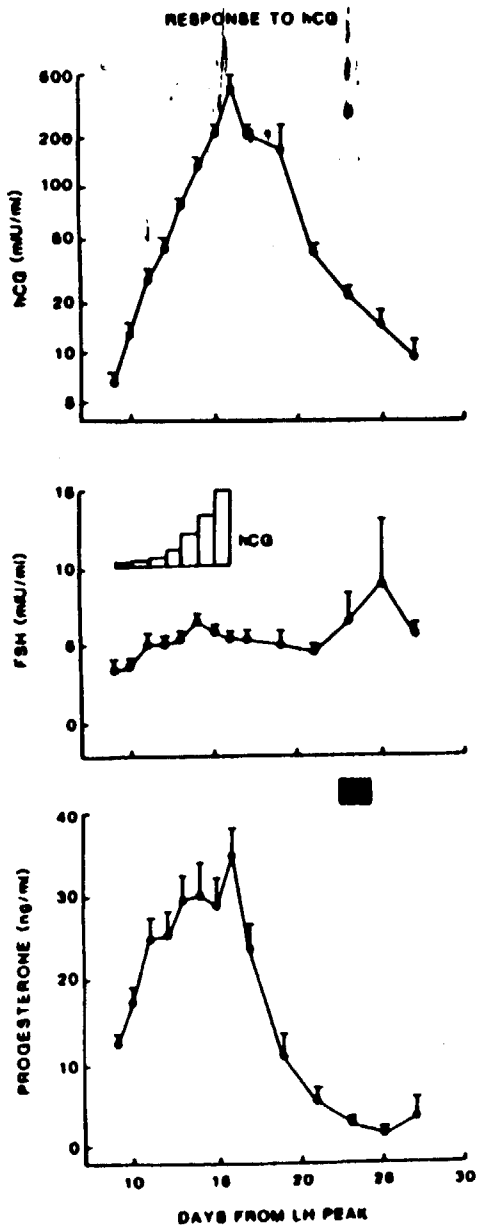
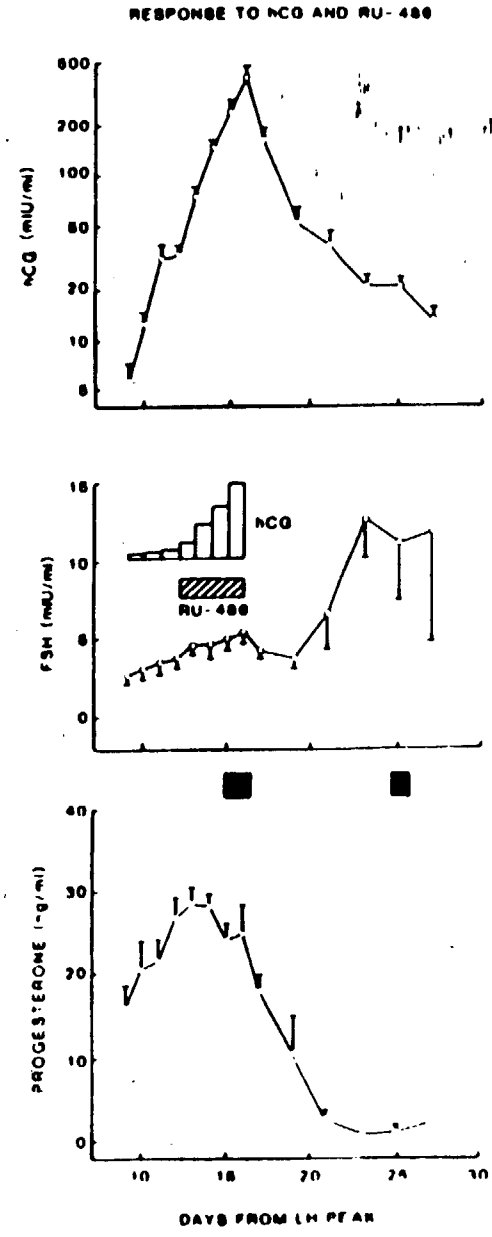


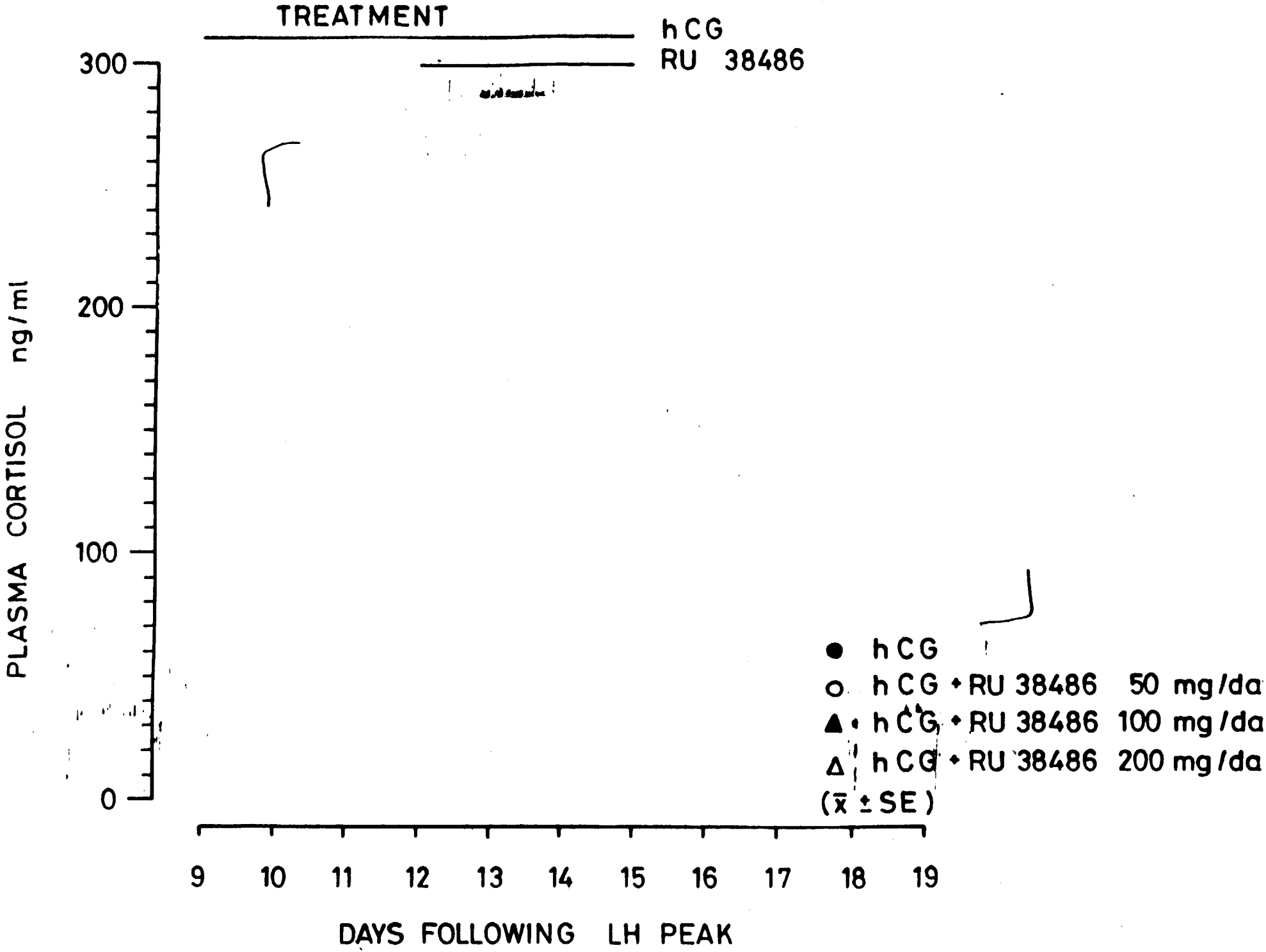
Fig 2

Fig. 1

Fig. 2







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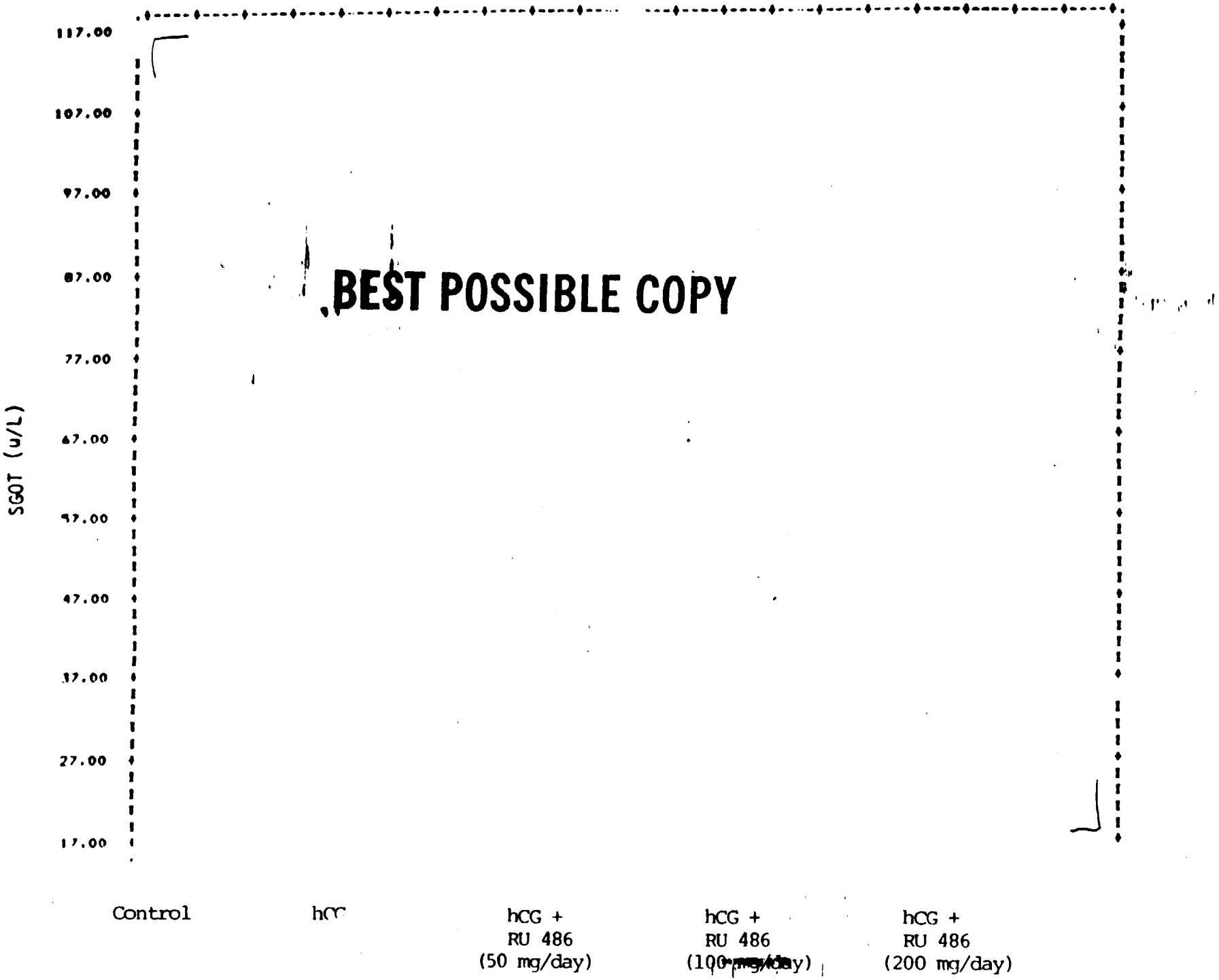

Fig 4

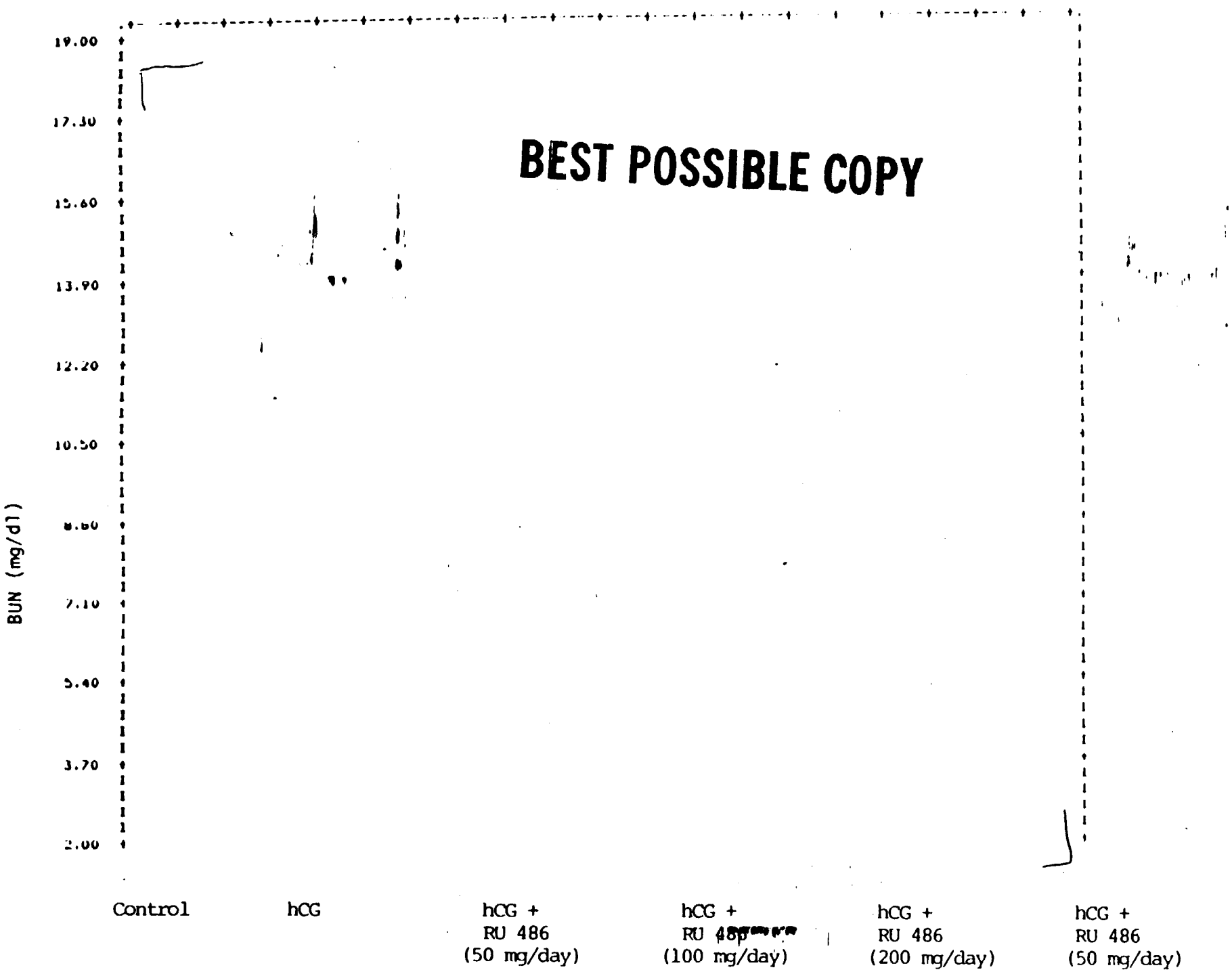

Fig 5

APR 15 1985

IND ———

The Population Council
Center for Biomedical Research
Attention: Irving M. Spitz, M.D.
1230 York Avenue
New York, New York 10021

Dear Dr. Spitz:

Please refer to your Notice of Claimed Investigational Exemption for a New Drug (IND) for RU 38486.

We also refer to your amendment dated December 7, 1984. We have completed our review of the data submitted and request that both hematological parameters and liver function be closely and carefully monitored in all patients receiving RU 38486.

Your cooperation is appreciated.

Sincerely yours,

/S/ 4/14/85

Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

cc:
IND Orig
HFN-810 — 4.12.85
HFN-810/ ——— /4/8/85; ——/4/10,12/85(1277D)
R/D init. by ———/4/8/85
Concurrence: ——————— /4/11/85
GENERAL CORRESPONDENCE

APPEARS THIS WAY
ON ORIGINAL

Copy filed in IND ——

The Population Council

Center for
Biomedical Research

1230 York A...
New York, New York 10021
Cable: Popbiomed, New York
Telephone (212) 570-8731
Telex: 238274 POBI UR

December 7, 1984

Division of Metabolism and
Endocrine Drug Products, HFN-130
Office of Biologics Research and Review
National Center for Drugs and Biologics
Department of Health and Human Services
Public Health Service
Rockville, MD 20857

Re: IND —— (RU 38486)

Dear ——

Enclosed please find this report on our Protocol 30 (single dose finding study of RU38486 in normal women).

Thanking you.

Sincerely yours,

Irving M. Spitz, M.D.
Coordinator Clinical Research

IMS:lm

See protocol II p. 74 of original submission to IND —— Amendment of 7-21-83 (to IND ——) of 2 new protocols (different location from protocol II) notifies us of the higher doses.

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DEC 14 1984
CENTER FOR DRUGS AND BIOLOGICS

MIF 004949

APPENDIX

Tolerance study of RU486 in normal women.

Study Design: Single doses of 50 mg, 100 mg, 200 mg, 400 mg, 600 mg and 800 mg of RU 38486 have been administered to normal women in the midluteal phase of their cycle. Five women were tested with each dose schedule.

Clinical Manifestations: These single doses produced no alterations in vital signs. In particular, supine and prone blood pressures remained constant. With the exception of the lowest dose, there was menstrual bleeding from 1 to 3 days following administration of RU 38486. This occurred at a time when progesterone levels ranged from 10-15 ng/ml. With all doses of RU 38486 up to 600 mg, menstrual bleeding occurred in association with the expected decrease in progesterone levels after a further 7 to 9 days. On the other hand with the 800 mg dose schedule, this bleeding was only evident in two out of 5 subjects but not in the remaining three subjects. This suggests that in the latter patients there had been complete endometrial shedding with the initial bleeding.

Hormone Response: There were no consistent alterations in LH, FSH, estradiol, nor progesterone levels. With the four highest doses, there was a transient dose dependent increase in prolactin levels although levels returned to normal 24 hours following RU 38486 administration (Fig. 1). There were no changes in serum cortisol except with the highest dose. In the latter instance, significantly raised levels were apparent twenty-four and forty-eight hours after RU 38486 administration (Fig. 2). ACTH levels were measured with the four highest doses and no changes were apparent (Fig. 3).

Drug Levels: Plasma RU 38486 levels were determined in a radioimmunoassay set up in Helsinki with reagents supplied by Rousell (Fig. 4). One hour after RU 38486 adminstration, there was no difference in drug levels with doses of 100, 200 and 400 mg; with the 50 mg dose, however, circulatory levels were lower. With the 50 and 100 mg doses of RU 38486 plasma levels remained stable for four hours and then decreased progressively. However, there were too few points to accurately determine the half disappearance time. On the other hand with doses of 200 and 400 mg RU 38486 plasma levels remained persistently elevated for up to 48 hours.

Hematological Finding (Tables 1-4) There were no consistent alterations in hematology. Analysis of variance showed a reduction of red blood cell count with doses of 600 milligram ($p<0.02$) and 400 milligram ($p<0.04$) but not with 800 mg. In five individual subjects, there was a reduction of hemoglobin at 24 and 48 hours after RU486 administration (Table 1). Similarly in four subjects, red blood cell count also showed a decrease below the normal range at the later time intervals (Table 2). It should be stated however that one of these subjects had a slightly reduced blood count and two had a reduced hemoglobin prior to drug administration. There was also a reduction in hematocrit at 24 and 48 hours in eight subjects but basal hematocrit was slightly reduced prior to treatment in two (Table 3). The slight reduction in hemoglobin, hematocrit and red cells noted at the latter time intervals, are unrelated to dose and cannot be attributed to blood loss from the venepunctures. In one subject given 600 milligram, white cell reduced to 2700 per mm although the initial count was only 3200 per mm (Table 4).

SMA Evaluation (Tables 5-9): SMA determinations also showed no consistent changes and only slight abnormalities of questionable significance were noted. Thus, analysis of variance showed that serum protein and albumin was reduced with the highest dose ($p < 0.03$) and blood urea nitrogen with a dose of 600 milligram ($p < 0.02$). However all individual values remained within the normal range. One subject had an increase in alkaline phosphatase although this was also evident in the basal samples (Table 5). Similarly bilirubin increased to 1.7 mg/dl in one subject receiving 600 milligram although values had decreased to the normal range after 48 hours (Table 6). Slight increases in inorganic phosphate were also evident in five subjects (Table 7). Basal pretreatment levels were increased in two of these and values had returned to normal by 48 hours in 4 (Table 8). CPK levels were also markedly increased in two subjects and SGPT in one (Table 9). In the latter three instances basal values prior to treatment had been elevated and this was therefore not related to the drug. It would thus appear that single doses produce no consistent alterations in SMA.

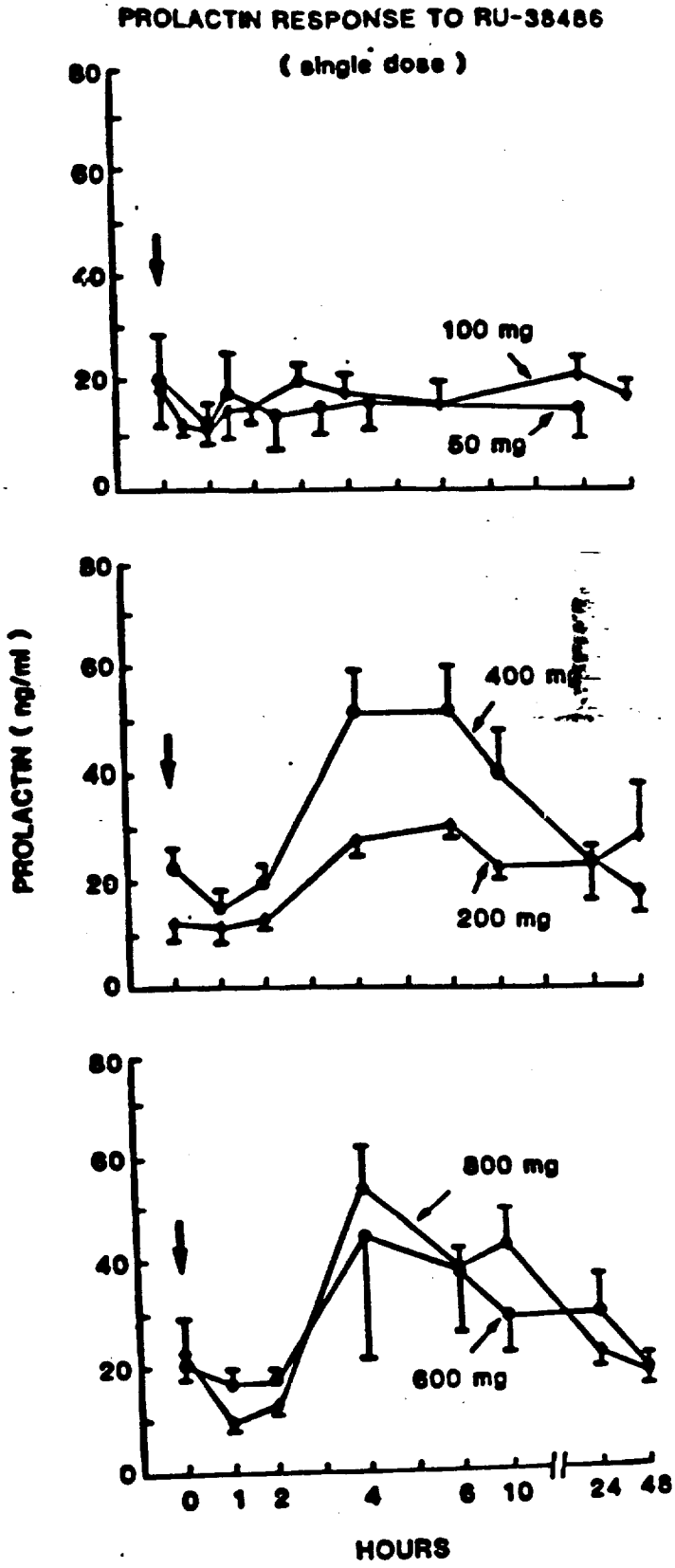


Fig. 1

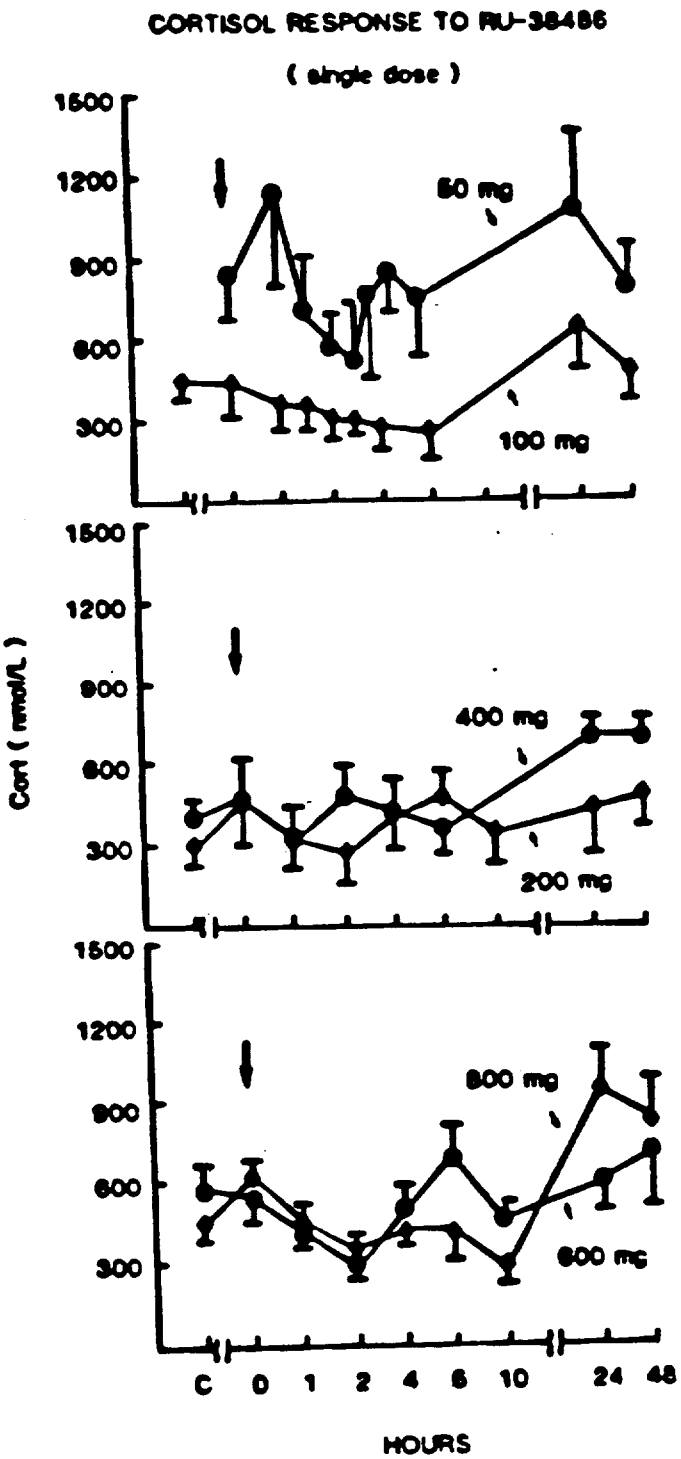
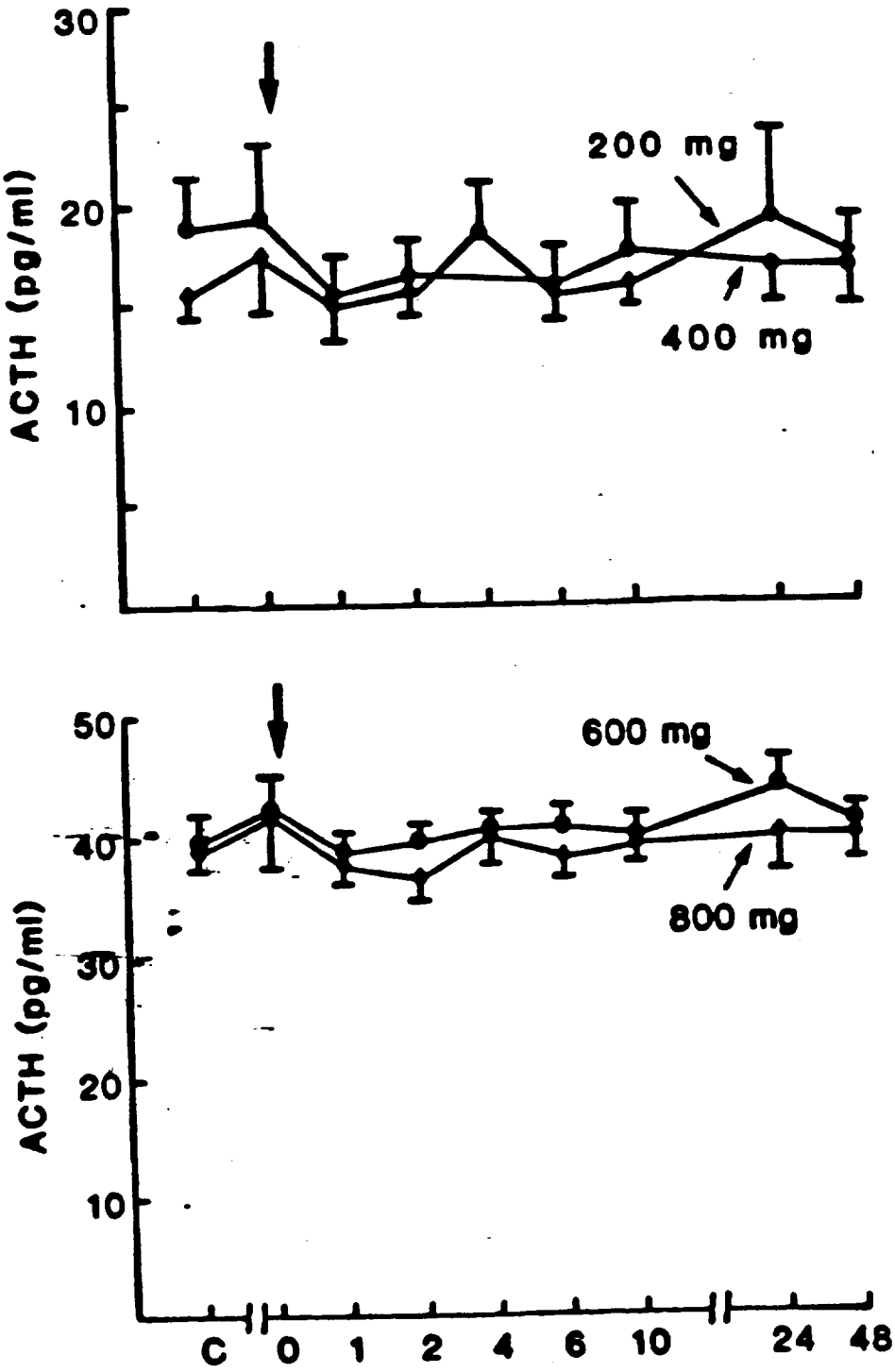


Fig. 2

ACTH RESPONSE TO RU-38486
(single dose)



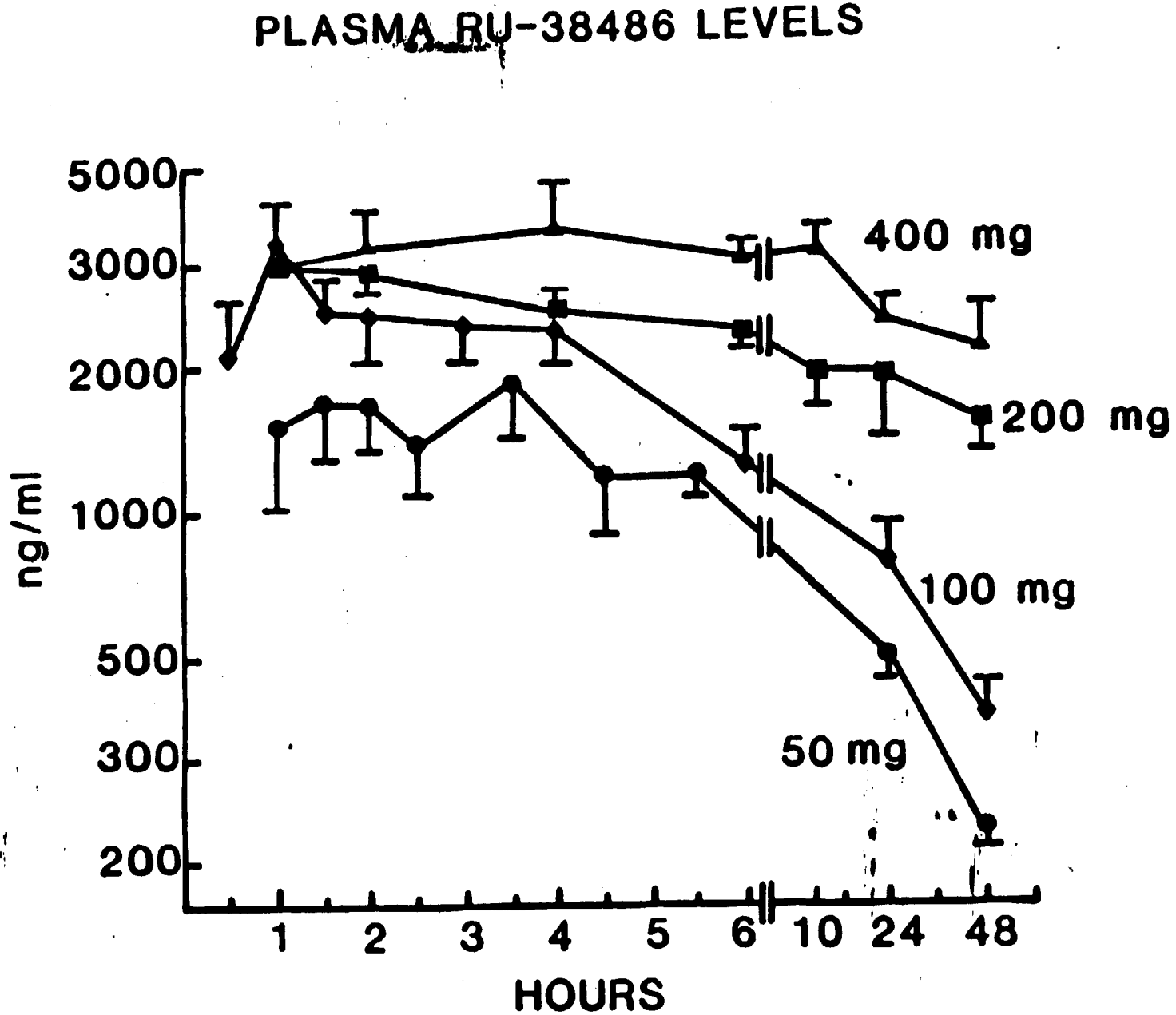


Fig. 4

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IND ——
IND ——

NOV 30 1984

The Population Council
Center for Biomedical Research
Attention: Irving M. Spitz, M.D.
Coordinator, Clinical Research
1230 York Avenue
New York, New York 10021

Dear Dr. Spitz:

Please refer to your Notices of Claimed Investigational Exemption for a New Drug (INDs) for RU 38486.

We also refer to your submission of October 23, 1984, to IND —— That amendment provided for a revised dosage schedule for your Los Angeles abortion study.

As noted in our October 1, 1984, letter to you, the two referenced INDs are for different indications. IND —— provides for the use of RU 38486 as an abortifacient, IND —— We have filed a copy of your October 23 amendment in IND —— Please address your future submissions to the appropriate IND number.

Sincerely yours,

/S/ 11.29.84

Consumer Safety Officer
Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

cc:
IND Orig's
HFN-810
HFN-810/ —— 11/14,28/84; ——11/28/84(7682C)
R/D init. ——— /11/14/84
GENERAL CORRESPONDENCE

The Population Council

Center for
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1230 York Avenue
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2-1

October 23, 1984

IND AMENDMENT

Division of Metabolism and
Endocrine Drug Products
National Center for Drugs
and Biologies
Food and Drug Administration
HFN 130
5600 Fishers Lane
Rockville, Maryland 20857

Re: IND on RU38486 (IND [redacted])

Dear [redacted]

We are currently pursuing our studies on pregant subjects in an attempt to induce an abortion with this agent in accordance with our protocol 32 which you have approved. In this protocol two different dose schedules were proposed, one for Los Angeles and a second for Uppsala. I was in telephonic communication with your office and informed them that we now wish to use the Uppsala protocol in Los Angeles. This is the administration of RU38486 in a dose of 50 mg twice a day for seven days.

I was informed that this would be in order and am merely writing to you to have this on record. When our full results of initial studies are available we will send you a comprehensive report.

With my best wishes.

Yours very sincerely,

Irving M. Spitz, M.D.
Coordinator
Clinical Research

IMS/rh

RECEIVED
HFN-810
NOV 6 1984
CENTER FOR DRUGS
AND BIOLOGICS

MIF 004958

he Population Council

nter for
omedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Telephone (212) 570-8731
Telex: 238274 POBI UR

/S/ 3/13/84

February 15, 1984

REVIEWS COMPLETED
CSO ACTION:
☐ LET. ☐ N.A.I.
/S/ 3/15/84
CSO INITIALS DATE

Food and Drug Administration
Division of Metabolism and
Endocrine Drug Products
National Center for Drugs
and Biologies
Food and Drug Administration
HFN 130
5600 Fishers Lane
Rockville, Maryland 20857

Re: IND 22047 for RU38486

Dear [redacted]

In reply to your letter on October 3rd, 1983, I enclose the dissolution test and specifications which you requested. I trust this is satisfactory.

Yours very sincerely,

Irving M. Spitz, M.D.
Coordinator
Clinical Research

Enclosure
IMS/rh

RECEIVED BUREAU OF DRUGS HFD-130 FEB 21 1984

21 CFR 50.25 ELEMENTS OF INFORMED CONSENT

(a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

(c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

(d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

RECORD OF TELEPHONE CONVERSATON/MEETING

DATE
Feb. 16, 1984

NDA NUMBER

IND NUMBER

TELECON/MEETING

INITIATED BY
☑ APPLICANT/SPONSOR
☐ FDA

MADE
☑ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME
RU 38486

FIRM NAME
The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Dr. Irving Spitz
Coordinator Clinical Research

TELEPHONE NO.
212-570-8731

On February 15, Dr. Spitz called to find out the status of the December 2 submission in which the progress of the ongoing studies were reported and protocols for further studies were submitted. ——— had received the submission late because the firm had confused the IND numbers (see my memo of telephone conversation with Dr. Spitz on January 24, 1984).

On February 16, I called Dr. Spitz and told him that the studies could proceed but we had comments concerning the informed consent form. I listed those to him and told him that we would follow with a letter.

He told me that they would soon be sending in an amendment to one of their protocols.

cc: Orig. IND
HFN137

SIGNATURE
HFN137 ——— 2/16/84
/S/

DIVISION
DMEDP

FORM FD 2587 (7/77)

ORIGINAL IND/NDA

MIF 004961

RECORD OF TELEPHONE CONVERSATON/MEETING

DATE: 1-24-84

NDA NUMBER:

IND NUMBER: ——— and ———

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☒ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: RU 38486

FIRM NAME: The Population Council

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr. Irving M. Spitz, Coordinator Clinical Research

TELEPHONE NO.: 212-570-8731

———— 2 of the protocols submitted to IND ——— on December, 1983, rec'd by FDA on Dec. 9, 1983, should have been submitted to IND ———, and therefore should have been reviewed by a different Medical Officer. The submission stated on the cover letter:

re: IND nos. ——— and ———
studies with RU 38486

I called Dr. Spitz and asked him to help clarify the matter. He stated that he made a mistake and the entire submission should have been submitted to IND ——— He said he thought the study under IND ——— had been completed and they would communicate with us on that later. He told me that it had been over 30 days since this information had been submitted & asked if he could initiate the study. I explained to him that because of the mistake the protocols had not been reviewed that I would see that the IND was given to the medical officer immediately, so that he could review it and that I would contact him by telephone and let him know when he can initiate the studies.

I copied the entire Dec 2 submission and added it to IND ———

SIGNATURE: /S/ CSO

DIVISION: DMEDP

FORM FD 2587 (7/77) ORIGINAL IND/NDA

MIF 004962

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Telephone (212) 570-8731
Telex: 238274 POBI UR

-signed
5/24/85
/S/

IND AMENDMENT

May 17, 1985

Division of Metabolism and Endocrine
Drug Products
National Center for Drugs and Biologies
Food and Drug Administration
HNA 130
5600 Fishers Lane
Rockville, Maryland 20257

Re: IND on RU38486 (IND

Dear

Enclosed please find 3 copies of two toxicological reports performed in the rat and monkey according to GLP practices.

Kind regards

Sincerely yours,

Irving M. Spitz, M.D.
Coordinator Clinical Research

IMS:smr

RECEIVED
MAY 23 1985
CENTER FOR DRUGS
AND BIOLOGICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 11 1993

IND [redacted]

The Population Council
Attention: Harold A. Nash
1230 York Avenue
New York, New York 10021

Dear Sir/Madam:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: [redacted]

Sponsor: The Population Council

Name of Drug: RU 38 486

Date of Submission: April 29, 1993

Date of Receipt: May 3, 1993

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

As Sponsor of the clinical study proposed in this IND, you are now free to obtain supplies of the investigational drug.

Should you have any questions concerning this IND, please call: [redacted]

Consumer Safety Officer
(301) 443- [redacted]

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
Bureau of Drugs, HFD-130
Attention: DOCUMENT CONTROL ROOM #14B-03
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours.

/S/

Division of Metabolism and Endorcrine
Drug Products
Bureau of Drugs

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228d (1/82)

IND —
IND —

SEP 19 1988

The Population Council
Center for Biomedical Research
Attention: Irving M. Spitz, M.D.
1230 York Avenue
New York, NY 10021

Dear Dr. Spitz:

Please refer to your Investigational New Drug Applications (INDs) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for the drug RU 486.

We have recently received a report of the occurrence of erythema multiforme in 3 normal male volunteers in a study of the effects of RU 38486 on immune function in normal volunteers and patients with hypercortisolism. The subjects received 10 mg/kg/day RU 486 for seven to fourteen days. So far, there have been no reports of this side effect in other studies which used RU 486 at higher doses or for longer periods in patients with hypercortisolism; nor have there been reports of erythema multiforme in normal volunteers treated with higher doses for less than one week.

Because of this newly reported side effect, we are requesting all sponsors of INDs for this drug to submit an interim safety update including a table of allergic reactions as soon as possible.

We appreciate your cooperation.

Sincerely yours,

/S/ 9/19/88

Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: IND Arch. (2)
HFD-510 (2)
HFD-511/ —— 8.3/8.7,15.33/ —— 9/8/88/ —— 9/16/88
—— 2286r/p.5
Concurrence: —— 8/11/88/ —— 8/12/88/
—— 9/8/88

INFORMATION REQUEST

IND ——

AUG 20 1987

The Population Council
Center for Biomedical Research
Attention: Irving M. Spitz, M.D.
Coordinator, Clinical Research
1230 York Avenue
New York, NY 10021

Dear Dr. Spitz:

Please refer to your Investigational New Drug Application (IND) for RU 38486.

We also refer to your progress report of July 17, 1987, our letter of April 15, 1985, and to telephone conversations on August 11 and 12, 1987, between you and —— of this Division.

We have reviewed your progress report, and we request the following additional information:

1. Please provide copies of figures 1 and 2, referenced in the progress report, which show hormonal values. We have not received the copies which you had mailed after submitting the report.

2. Please submit the detailed analysis of SMA and hematologic profiles from all three clinics as soon as it is available.

3. Please send us a brief description of your general investigational plan for the next year.

Your cooperation is appreciated.

Sincerely yours,

/S/ 8/19/87

——

Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: IND Orig.
HFN-810
HFN-810 ——
HFN-810 —— /8.18.87 —— 6438R)
Concurrences: —— 8/19/87/

/S/ 8/19/87

INFORMATION REQUEST

Progress Report

IND AMEND #011

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Telephone (212) 570-8731
Telex: 238274 POBI UR

#011

March 20, 1986

Division of Metabolism and Endocrine
Drug Products, HFN-130
Office of Biologics Research and Review
National Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: INT ——— for RU486

Dear ———

Enclosed please find an interim summary of the results available on abortion induction with RU486 in subjects studied in Los Angeles, Paris and Uppsala. A final report will be submitted when all centers have enrolled and evaluated all subjects.

Thanking you.

Yours very sincerely,

I Spitz

Irving M. Spitz, M.D.
Coordinator
Clinical Research

RECEIVED
HFN-810 COMPLETED
MAR 27 1986
CENTER FOR DRUGS
AND BIOLOGICS

☒ N.A.I.
7.21.86
DATE

MIF 004967

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Telephone (212) 570-8731
Telex: 238274 POBI UR

IND ...NT

Noted
11/7/85
JSI

October 28, 1985

Division of Metabolism and
Endocrine Drug Products, HFN-130
Office of Biologics Research and Review
National Center for Drugs and Biologics
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Rockville, MD 20857

Re: IND for RU486 IND number

Dear

To date we are using RU486 for induction of abortion according to our established protocols. We have now treated 125 subjects with RU486 100 milligram per day for 7 days and have obtained a complete abortion in 95 subjects. With a dose of 50 milligram per day for 7 days the success rate is only about 51 percent. However we have only studied about 40 cases.

In Paris Roussel are now using 450 milligram and 600 milligram on a one time basis for abortion induction. Like our protocol, this regimen produces minimum side effects. We would therefore like to amend our IND by adding these two dose regimens. viz. 450 milligram or 600 milligram on a one time basis for abortion induction. We plan to study 150 subjects with each dose.

With my best wishes.

Yours very sincerely,

Irving M. Spitz, M.D.
Coordinator
Clinical Research

RECEIVED
HFN-810
NOV 4
CENTER FOR DRUGS AND BIOLOGICS

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☒ N.A.I.

/S/ 11-7-85
CSO INITIALS DATE

MIF 004968

The Population Council
Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Facsimile: (212) 570-7678
Telephone: (212) 570-8731
Telex: 238274 POBI UR

March 3, 1989

REVIEWS COMPLETED
3/20/89

CSO ACTION:
☒ LETTER ☐ N.A.L.
/S/ 5/8/89
CSO INITIALS DATE

Division of Metabolism
and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: IND — for RU 486

Dear —

This is a further progress report of our studies on abortion induction with RU 486. The Swedish group in Uppsala have now administered RU 486 in a dose of 20 mg/day for 7 days. These results are shown in Tables I-V. An article has been published in Contraception and this is enclosed in the appendix. Results on the dosage of 100 mg/day for seven days and 50 mg/day for seven days have already been submitted to your office. They are nevertheless included in this interim summary so that the data can be compared to the lowest dose schedule (20 mg/day for seven days) which is the subject of the present report.

In this Swedish study, RU 486 was administered in doses of 20 mg, 50 mg, and 100 mg daily for 7 days. The three groups were matched for age, weight, duration of amenorrhea, and previous obstetrical history (Table I). The incidence of complete abortion was 73% with the 20 mg dose, 66% with the 50 mg dose, and 64% with the 100 mg dose (Table II). There was no significant difference between the responses. The onset of bleeding occurred at 2.4 ± 0.7 (SD) days with the intermediate and high dose but was delayed to 3.5 ± 1.2 days with the lowest dose. Passage of products of conception occurred at 3.5 days with the two higher doses and at 5.1 days with the lowest dose. The reduction in hemoglobin was greatest with the lowest dose regimen (134.8 g/l pretreatment versus 122.7 g/l post-treatment). With the other two dose schedules there was no change in hemoglobin (Table III). Side effects were similar with the three dose regimens although it was apparent that the incidence of nausea was somewhat higher with the lowest dose (Table IV). In all three groups, women who aborted had significantly lower pretreatment levels of βhCG than women who had incomplete abortions or continuing pregnancy (Table V). There was, however, no significant difference in progesterone or estradiol levels in those who aborted or failed to abort (Table V). Treatment was well tolerated by all women except for one woman with the lowest dose regimen who experienced a profound bleeding episode necessitating blood transfusion.

We are no longer performing any studies with RU 486 in Paris, France.

Dr. Mishell in Los Angeles, however, is pursuing studies on RU 486 administration. He is now doing a comparative study administering RU 486 followed by either a further dose of RU 486 or a prostaglandin. Too few subjects have been studied for meaningful results. A full summary will be submitted to your office at a later date.

When the SMA and hematology results have been analyzed by our statisticians they will be forwarded to your office.

Kind regards and best wishes.

Sincerely yours,

Irving M. Spitz, M.D.
Coordinator
Clinical Research

IMS:dm

Enclosure

APPEARS THIS WAY
ON ORIGINAL

TABLE I

Background data on women treated with RU 486, 10, 25 and 50 mg x 2, respectively, for 7 days in early pregnancy, mean (SD).

	10 mg x 2	25 mg x 2	50 mg x 2
Age (years)	31.2 (7.3)	30.6 (7.2)	30.2 (6.5)
Weight (kg)	60.1 (7.9)	60.6 (8.3)	57.9 (7.1)
Days from LMP	43.5 (4.2)	44.2 (3.9)	44.3 (4.0)
Primigravidae (#)	42	44	53
Induced abortion (#)	42	23	30
Spontaneous abortion (#)	10	8	8

TABLE II

Clinical results in 48, 52 and 53 women treated with RU 486, 10, 25 and 50 mg x 2, respectively, for 7 days in early pregnancy.

	10 mg x 2	25 mg x 2	50 mg x 2
n	48	52	53
Complete abortion	35 (73%)	34 (66%)	34 (64%)*
Incomplete abortion	1	2	6
Continuing pregnancy	12*	16**	13*

TABLE III

Bleeding patterns in women responding with complete abortions after treatment with RU 486, 10, 25 and 50 mg x 2, respectively, for seven days in early pregnancy, mean (SD).

	10 mg x 2	25 mg x 2	50 mg x 2
Onset of bleeding (d)	3.5 (1.2)	2.4 (0.7)	2.4 (0.7)
Passage of products (d)	5.1 (1.2)	3.5 (0.8)	3.5 (1.2)
Duration of bleeding (d)	11.4 (3.6)	12.3 (3.5)	11.3 (3.6)
Range of duration (d)	6-23	6-20	6-20
Hb pre (g/l)	134.8 (8.9)	129.6 (7.5)	131.7 (10.3)
Hb post (g/l)	122.7 (14.5)	124.5 (10.8)	125.3 (11.3)

TABLE IV

Subjective side effects during treatment with RU 486, 10, 25 and 50 mg x 2, respectively, for 7 days in early pregnancy.

	10 mg x 2	25 mg x 2	50 mg x 2
Abdominal pain	3	4	8
Nausea	18	14	8
Vomiting	5	5	2
Headache	2	3	3

TABLE V

Pretreatment plasma levels of hCG, progesterone and estradiol and gestational length in women who responded with complete abortion and others (incomplete abortion or continuing pregnancy) during treatment with RU 486, 10, 25 and 50 mg x 2, respectively, for 7 days in early pregnancy. Mean (SEM).

	Complete abortions	Others
RU 10 mg x 2		
n	35	13
hCG	20173 (3170)	43907 (8390) (p<0.01)
progesterone	46.8 (4.0)	46.8 (5.3)
estradiol	1221 (110)	1802 (291)
days from LMP	42.9 (0.8)	44.8 (0.9)
RU 25 mg x 2		
n	34	18
hCG	25335 (4746)	52475 (7777) (p<0.01)
progesterone	40.6 (3.5)	36.8 (3.9)
estradiol	1614 (194)	2255 (382)
days from LMP	43.5 (0.7)	45.6 (0.8)
RU 50 mg x 2		
n	34	19
hCG	24333 (4548)	47589 (9731) (p<0.05)
progesterone	43.8 (3.0)	47.6 (4.6)
estradiol	1504 (119)	2126 (357)
days from LMP	44.1 (0.7)	44.8 (0.8)

Appendix

Birgerson, L., and Odlind, V. The antiprogestational agent RU 486 as an abortifacient in early human pregnancy: A comparison of three dose regimens. Contraception 38(4):391-400, 1988.

THE ANTIPROGESTATIONAL AGENT RU 486 AS AN ABORTIFACIENT IN EARLY HUMAN PREGNANCY: A COMPARISON OF THREE DOSE REGIMENS

Lars Birgerson and Viveca Odlind

Department of Obstetrics and Gynaecology, Uppsala University, Akademiska Sjukhuset, S-751 85 Uppsala, Sweden

ABSTRACT

Three different regimens of RU 486, a progesterone receptor blocking agent, were compared for their ability to terminate early human pregnancy. One-hundred-fifty-three healthy women with a gestational length less than 49 days from the last menstrual period were recruited to the study and randomly allocated to one of three treatment regimens: 1) RU 486 10 mg x 2 for seven days; 2) RU 486 25 mg x 2 for seven days; or 3) RU 486 50 mg x 2 for seven days. No significant difference in efficacy was seen between the three dose regimens. Treatment with 10 mg x 2 x VII resulted in 73 per cent complete abortions, 25 mg x 2 x VII in 66 per cent and 50 mg x 2 x VII in 64 per cent complete abortions. Response to treatment, measured as reported onset of bleeding and passage of products of conception, however, occurred significantly later on the 10 mg x 2 regimen than on the other two dose regimens. In each treatment group, women who subsequently aborted completely had significantly lower pretreatment levels of hCG than women with incomplete abortion or continuing pregnancy. The treatment was well tolerated by the women and except for one woman who experienced a profound bleeding necessitating a blood transfusion, no serious side effects were seen.

Submitted for publication June 16, 1988
Accepted for publication July 21, 1988

INTRODUCTION

The ability of RU 486 to shorten the luteal phase and interrupt early human pregnancy was first reported by Hermann et al. (1). The abortifacient properties of this compound, which is a receptor blocking agent with affinity preferably for the progesterone and the glucocorticoid receptors, have later been confirmed by several investigators. These studies, using different dose regimens, have resulted in frequencies of complete abortions ranging from 10 to 88 per cent (2-8). A common feature in these studies is lack of a clear dose-response relationship. Increased dosage sometimes paradoxically resulted in a decrease in the rate of complete abortions (5,7). Another feature in these studies is the small number of women treated with each dose regimen.

The aim of the present study was to compare the effects of three different dose regimens, 10, 25 and 50 mg x 2, respectively, for seven days in early pregnancy.

MATERIALS AND METHODS

Subjects

One-hundred-fifty-three women, less than 49 days pregnant as judged from the last menstrual period, volunteered for the study after thorough information about the purpose and design of the study. The women all had regular menstrual cycles and were certain of the date of their last menstruation. The inclusion criteria also included a positive pregnancy test, a pelvic examination revealing a uterus of expected size for the reported time of gestation, and an apparently normal pregnancy. Patients with any signs of abnormal pregnancy, a history of repeated spontaneous abortions, liver, renal or gastrointestinal disease, or recent (less than 3 months) use of glucocorticoids in any form, were excluded from the study.

Study Protocol

The patients participating in the study were recruited consecutively from among women applying for termination of early pregnancy. At the first visit, on day 0, the patients underwent a physical examination and blood samples were collected for the analysis of human chorionic gonadotrophin (hCG), progesterone, estradiol and cortisol. Blood was also obtained for analysis of hematology, electrolytes, liver and kidney function tests and albumin. The women were randomly allocated to one of the three treatment regimens. A preliminary time for vacuum aspiration in case of treatment failure was arranged 8 to 10 days after the onset of treatment. The patients were instructed to take the tablets (supplied by Roussel-Uclaf, Romainville, France) at 8.00 am and 6.00 pm daily and to withhold food for one hour before and after drug administration. Follow-up visits were scheduled on days 7, 14 and 42. At the first follow-up visit on day 7, the

patients were examined again and the same blood sampling as on day 0 was repeated. If the patient showed no sign of abortion, a vacuum aspiration was performed but if the patient was considered to have aborted, she returned on day 14, when an evaluation was made whether the abortion was complete or not. Blood samples for analysis of hCG and steroid hormones were collected again. To be classified as having had a complete abortion at this visit, the patients' hCG levels should have decreased to <10 per cent of the initial value. The uterus should be back to normal size and the bleeding should have ceased or be minimal. At the last visit, on day 42, the patient's opinion of the treatment, the total duration of bleeding and her choice of family planning method for the future were obtained.

Hormone Assays

Plasma concentrations of hCG (Wallac Oy), progesterone (9), estradiol (10) and cortisol (Farmos Oy) were determined by radioimmunoassays.

Statistics

Statistical significance was assessed by Student's t-test for dependent and independent observations, chi-square test, analysis of variance and regression analysis (11).

RESULTS

The women in the three treatment groups did not differ significantly in age, weight, gestational length, parity or frequency of previous induced or spontaneous abortions (Table I).

Table I. Background data on women treated with RU 486, 10, 25 and 50 mg x 2, respectively, for 7 days in early pregnancy, mean (SD)

	10 mg x 2	25 mg x 2	50 mg x 2
n	48	52	53
Age (years)	31.2 (7.3)	30.6 (7.2)	30.2 (6.5)
Weight (kg)	60.1 (7.9)	60.6 (8.3)	57.9 (7.1)
Days from LMP	43.5 (4.2)	44.2 (3.9)	44.3 (4.0)
Primigravidae (%)	27	33	40
Nulliparae (%)	42	44	53
Induced abortion (%)	42	23	30
Spontaneous abortion (%)	10	8	8

Clinical results

Treatment with 10 mg x 2 resulted in 73 per cent complete abortions, with 25 mg x 2 in 66 per cent and with 50 mg x 2 in 64 per cent complete abortions. After corrections were made for the 5 patients who discontinued therapy, the results were 74, 68 and 65 per cent complete abortions, respectively. These differences were not statistically significant. One, two and six women, respectively, experienced incomplete abortions with inadequate involution of the uterus and only partial decrease of hGC levels, while in 12, 16 and 13 women, respectively, the pregnancies continued with only a scanty vaginal bleeding and rising hGC levels (Table II).

Table II. Clinical results in 48, 52 and 53 women treated with RU 486, 10, 25 and 50 mg x 2, respectively, for 7 days in early pregnancy

	10 mg x 2	25 mg x 2	50 mg x 2
n	48	52	53
Complete abortion	35 (73%)	34 (66%)	34 (64%)*
Incomplete abortion	1	2	6
Continuing pregnancy	12*	16**	13*

* One patient discontinued
** Two patients discontinued

There were no statistically significant differences between the patients who aborted completely and the others regarding age, weight, gestational length, parity or frequency of previous induced abortions or previous spontaneous abortion.

Except for one woman, treated with 10 mg x 2, all women responded to treatment with a vaginal bleeding.

Among patients experiencing a complete abortion, the women in the 25 mg x 2 and 50 mg x 2 groups noted the same mean duration between start of medication and response. In both these groups a vaginal bleeding started after 2.4 days while passage of products was reported after 3.5 days. The women treated with 10 mg x 2 responded significantly later with onset of bleeding after 3.5 days and passage of products after 5.1 days ($p<0.001$; Table III).

Among women aborting completely, the bleeding was in most cases reported as scanty for a day or two, followed by a heavier bleeding, more than a normal menstruation for 3-4 days, and then again scantier for the remainder of the bleeding period.

The duration of bleeding in patients with a complete abortion was similar with the three treatment regimens with a mean duration of 11.3 to 12.3 days (Table III). No difference was found in mean reduction of hemoglobin between the women in the 25 mg x 2 and 50 mg x 2 groups, while the women in the 10 mg x 2 group showed a slightly greater decrease in hemoglobin post-treatment ($p<0.05$; Table III). One patient, treated with 10 mg x 2, experienced a profound bleeding with hemoglobin post-treatment decreasing to 76 g/l necessitating a blood transfusion. No such problems were seen in the other two treatment groups.

Table III. Bleeding patterns in women responding with complete abortions after treatment with RU 486, 10, 25 and 50 mg x 2, respectively, for seven days in early pregnancy, mean (SD)

	10 mg x 2	25 mg x 2	50 mg x 2
Onset of bleeding (d)	3.5 (1.2)	2.4 (0.7)	2.4 (0.7)
Passage of products (d)	5.1 (1.2)	3.5 (0.8)	3.5 (1.2)
Duration of bleeding (d)	11.4 (3.6)	12.3 (3.5)	11.3 (3.6)
Range of duration (d)	6-23	6-20	6-20
Hb pre (g/l)	134.8 (8.9)	129.6 (7.5)	131.7 (10.3)
Hb post (g/l)	122.7 (14.5)	124.5 (10.8)	125.3 (11.3)

Side effects

The subjective side effects reported by the patients were generally mild. Nausea dominated, especially in the 10 mg x 2 group, where it was significantly more common than in the 50 mg x 2 group ($p<0.05$). This symptom in most cases appeared 24-36 hours after start of treatment. Patients, who had been pregnant in the past, described it as pregnancy nausea that was only slightly more intense than "normal" but in some cases the symptoms were more severe and associated with vomiting. This was also the reason for discontinuation of treatment in five cases. Some patients reported lower abdominal pain, described as slightly more intense than their "normal" menstrual pain (Table IV).

Table IV. Subjective side effects during treatment with RU 486, 10, 25 and 50 mg x 2, respectively, for 7 days in early pregnancy

	10 mg x 2	25 mg x 2	50 mg x 2
Abdominal pain	3	4	8
Nausea	18	14	8
Vomiting	5	5	2
Headache	2	3	3

The changes observed in the routine laboratory screening performed before and after treatment were very slight, and well within the normal limits. At the follow-up visit, 89, 83 and 83 per cent of the women, respectively, in the three groups stated that they were satisfied with the treatment and would be prepared to receive it again, should they ever again want an abortion.

Hormonal results

No significant differences were noted between the three groups in pretreatment plasma levels of hCG, progesterone, estradiol or cortisol.

Plasma levels of hCG, progesterone and estradiol were markedly depressed on day 7 compared to before treatment in women who aborted completely on all three treatment regimens. Patients with incomplete abortions showed a less marked decrease in hCG, while progesterone and estradiol in these patients remained unaltered. Women with a continuing pregnancy showed increased plasma levels of hCG and estradiol on day 7, whereas progesterone levels did not change.

When pretreatment levels of hCG were compared, women who responded with a complete abortion had significantly lower levels than the others in all three treatment groups (Table V). In the 10 mg x 2 group, 63 per cent of the women who subsequently aborted completely had a pretreatment value of hCG <18,000 IU/l as compared to 30 per cent among the others. The corresponding figures for the 25 mg x 2 group were 55 and 12 per cent and for the 50 mg x 2 group 61 and 26 per cent, respectively.

Also, pretreatment levels of estradiol were lower, however not significantly so, in women with complete abortions compared to others in all three groups, whereas there were no such differences in pretreatment levels of progesterone in any of the treatment groups (Table V).

When all 153 women in this study were classified according to outcome of treatment, disregarding dose regimen, pretreatment levels of both hCG ($p<0.001$) and estradiol ($p<0.01$) were

significantly lower, and the gestational length ($p<0.05$) was shorter in women who subsequently aborted completely whereas there was no significant difference in pretreatment levels of progesterone.

In all three treatment groups, plasma levels of cortisol were significantly elevated on day 7 compared to before treatment ($p<0.001$). On day 14 plasma levels of cortisol were nearly back to pretreatment levels in the 25 mg x 2 and 50 mg x 2 groups ($p<0.001$ compared to day 7), whereas the decrease was less pronounced in the 10 mg x 2 group ($p<0.05$). Thus, on day 14, the plasma cortisol levels of the women in the 10 mg x 2 group were higher than in the other two treatment groups ($p<0.01$).

There was no correlation between cortisol levels and any reported subjective discomfort. Pretreatment cortisol levels did not differ between women who subsequently aborted completely and the others.

Table V. Pretreatment plasma levels of hCG (IU/l), progesterone (nmol/l) and estradiol (pmol/l) and gestational length (days from LMP) in women who responded with complete abortion and others (incomplete abortion or continuing pregnancy) during treatment with RU 486, 10, 25 and 50 mg x 2, respectively, for 7 days in early pregnancy; Mean (SEM)

	Complete abortions	Others	
RU 10 mg x 2			
n	35	13	
hCG	20,173 (3170)	43,907 (8390)	p<0.01
progesterone	46.8 (4.0)	46.8 (5.3)	
estradiol	1221 (110)	1802 (291)	
days from LMP	42.9 (0.8)	44.8 (0.9)	
RU 25 mg x 2			
n	34	18	
hCG	25,335 (4746)	52,475 (7777)	(p<0.01)
progesterone	40.6 (3.5)	36.8 (3.9)	
estradiol	1614 (194)	2255 (382)	
days from LMP	43.5 (0.7)	45.6 (0.8)	
RU 50 mg x 2			
n	34	19	
hCG	24,333 (4548)	47,589 (9731)	(p<0.05)
progesterone	43.8 (3.0)	47.6 (4.6)	
estradiol	1504 (119)	2126 (357)	
days from LMP	44.1 (0.7)	44.8 (0.8)	

DISCUSSION

The rate of complete abortions obtained with the two higher dose regimens used in this study, 25 mg x 2 and 50 mg x 2, respectively, corresponds well with previous studies where comparable daily doses have been used (2,3,5-8). The lack of difference in efficacy between these two dose regimens is also in accordance with previous observations (5,6).

The efficacy of the lowest daily dose used in this study, 10 mg x 2, has not been investigated before. Although the complete abortion rate with this dose did not differ from that of the higher doses, the significantly later response to treatment with the lowest dose, measured as mean duration from start of therapy to onset of bleeding and passage of products, might very well reflect a dose-response relationship which earlier studies have failed to demonstrate.

Couzinet et al. reported 85 per cent complete abortions when treatment was limited to pregnant women not more than 10 days after the missed period, and when women with plasma hCG levels above 18,000 IU/l were excluded (8). Using these strict criteria for selection of eligible patients, they could not demonstrate any differences in levels of hCG, progesterone or estradiol or gestational length between women who aborted and those who did not (8). In the present study, however, into which patients were eligible through the 7th week of pregnancy, a correlation was demonstrable between pretreatment hCG, estradiol and days from last menstrual period and outcome of therapy. However, if only women with pretreatment hCG levels below 18,000 IU/l were considered in the present study, the rate of complete abortions was 85 per cent, a figure identical to that reported by Couzinet et al. (8).

When the parameters, pretreatment levels of hCG, progesterone, estradiol, cortisol and gestational length, were analyzed by stepwise logistic regression, considering all 153 women together, pretreatment level of hCG was found to be the best predictor of outcome of treatment with a sensitivity of 92.6 per cent, a figure that did not improve when the other parameters were added. Thus, the results of this study support previous suggestions that the efficacy of RU 486 depends on the hCG levels which in turn probably reflect the true gestational length.

The rate of complete abortions obtained in this study and the lack of difference in efficacy between the three doses used do not support the possibility of RU 486 alone being a realistic alternative to vacuum aspiration as a method for termination of human pregnancy up to 7 weeks of gestation. As has been suggested earlier by Swahn et al. (12), the use of RU 486 as an abortifacient at this stage of the first trimester will probably require the addition of a uterotonic agent to achieve a satisfying frequency of complete abortions. However, the results obtained in this study indicate that a uterotonic agent could be combined with a lower dose of RU 486 than what has been used in previous studies (12,13).

ACKNOWLEDGEMENTS

This study was undertaken as part of the contraceptive development program sponsored and coordinated by the International Committee for Contraception Research of the Population Council, New York, N.Y., U.S.A. The financial support provided by the Swedish Medical Research Council (grant no. 3495), the Rockefeller Foundation and Mellon Foundation is gratefully acknowledged. The provision of drugs from Roussel-Uclaf, Romainville, France, is also gratefully acknowledged.

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IND ——

JAN 14 1992

The Population Council
Attention: Irving M. Spitz, M.D.
Center for Biomedical Research
1230 York Avenue
New York, NY 10021

Dear Dr. Spitz:

Please refer to your Investigational New Drug Application (IND) for the preparation RU 486 (mifepristone) Tablets, IND ——

We also refer to your letter dated November 19, 1990.

We have completed our review of your submission and have the following comments and information requests:

1. We call your attention to an error in Table 4. The correct percentage of women experiencing salpingitis is 0.01%, rather than 0.09% as stated.

2. Since hypotension, when it does occur, is known to occur within the first four hours after administration of the prostaglandin, it may be prudent to consider modifying your protocol so that patients remain under medical monitoring and supervision for at least four hours after administration of the prostaglandin.

3. Is there an explanation for the rather high percentage of blood transfusions administered in the United Kingdom?

If you should have any questions concerning this IND, please contact

Sincerely yours,

/S/ 1/13/92

Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: IND Arch /S/ 1.14.92
HFD-510
HFD-510/ ——
HFD-510/ —— 12.24.91/FT/1/14/92/
Concurrences: —— /1/13/92/

INFORMATION REQUEST

IND ——

MAY 9 1989

The Population Council
Attention: Irving Spitz, M.D.
Coordinator, Clinical Research
Center for Biomedical Research
1230 York Avenue
New York, NY 10021

Dear Dr. Spitz:

Please refer to your Investigational New Drug Application (IND) for the preparation RU 38486.

We also refer to your annual report dated March 3, 1989.

We look forward to receiving the SMA and hematology results from the Uppsala study after they have been analyzed by your statisticians. This information is important because earlier tolerance studies using single doses of up to 600 to 800 mg RU 486 revealed a few subjects with reductions of hemoglobin, hematocrit, and red blood cell counts, one with a reduction of her albumin, one patient with a reduction of blood urea nitrogen, one subject with bilirubin, a few subjects with marked increases in CPK levels and one subject with a marked increase in SGPT. These changes prompted us to request that hematology and liver function be carefully and closely monitored in all subjects receiving the drug in your studies.

[redacted]

Sincerely yours,

5/8/89

———/ /

Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

5-8-89

/Sl/

cc: IND Arch. ——
HFD-510
HFD-510/ ——
HFD-510/ —— 5.1,2.80/ft/ —/5/3/89/ ——3226r
Concurrences: ———— 5/2/89/

GENERAL CORRESPONDENCE - GC

The Population Council
Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
Facsimile: (212) 570-7678
Telephone: (212) 570-8731
Telex: 238274 POBI UR

Noted
10/25/91
/S/

October 16, 1991

Noted
/S/
10/28/91

Division of Metabolism and
Endocrine Drug Products, HFD-510
Center For Drug Evaluation and Research
Document Control Rm. ———
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

/S/

Re: IND ——— RU 486

Dear ———

It was good talking to you on the telephone the other day. As I mentioned to you, we allow cross-indexing of our IND ——— for RU 486 to all investigators provided this is authorized by Roussel-UCLAF. These investigators have to submit their own IND and make the required reports to the FDA. In accordance with the policy of Roussel-UCLAF, the investigators may cross-index to all pre-clinical studies of RU 486 as well as the manufacturing details and toxicology present in our IND.

I hope this will answer all your questions. Should you have any further queries, please do not hesitate to contact me.

Sincerely yours,

Irving M. Spitz, M.D.
Coordinator
Clinical Research

cc: H. Nash
F. Schmidt

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER
☒ N.A.I.
/S/
10-30-91
INITIALS
DATE

MIF 004985

The Population Council
Center for
Biomedical Research

1230 York Avenue
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Noted 2/11/91 /S/

NDEC ORIGINAL

February 1, 1991

Division of Metabolism and Endocrine Drug Products
HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG REC'D FEB 0 5 1991 HFD-510 EVALUATION AND RESEARCH

Re: IND ———

Dear ———

This is in reply to your letter of 17 January 1991 requesting that we outline steps to prevent studies being undertaken without protocol submission to the FDA. Our routine controls are those of requiring 1) a signed protocol 2) a 1572 form with identification of all investigators 3) proof of approval by the local Human Research Committee 4) approval by the Council's IRB before shipping supplies of drug. Additionally, visits by a clinical monitor are scheduled at regular intervals.

We have recently reemphasized to investigators that they submit to us record forms for all patient visits once a month. Telephone follow-up is instituted if records are more than 2 months overdue. We have also introduced into our record forms a question as to whether blood samples were taken this visit. This alerts us to investigations that may not have been part of the protocol and which require blood samples.

Finally, we will send a letter to all investigators emphasizing the necessity of formally submitting to us for submission to the FDA and to our Institutional Review Board any planned protocol modifications or additions.

Sincerely yours,

C. Wayne Bardin

C. Wayne Bardin, M.D.
Director

CWB:ma

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☒ N.A.I.
/S/ 2-11-91
CSO INITIALS DATE

IND [redacted]
RU-486 (mifepristone)
Population Council

July 16, 1993

Memorandum of Meeting

Population Council Representatives:
Rosemarie Thau
Irving Spitz
Ann Robbins
Irving Sivin
Wayne Bardin

FDA Staff:

[redacted] CSO
[redacted] (GCF-1)
[redacted] (HFD-713)

Purpose: Requested by the Division to discuss the development plan and time frame for RU-486.

Discussion and Conclusions:

The Population Council has received 40 volumes of clinical data from Roussel Uclaf. Although the data provides information on 150,000 women, only 1200 women used RU-486 with the prostaglandin, Cytotec. The Population Council intends to amend their current IND [redacted] with the proposed U.S. clinical trial, an updated Investigator's Brochure, and the updated CMC and toxicology information. The NDA will be submitted with data from a completed French study and the U.S. study. The NDA will initially be submitted with labeling reflecting current use in France, indicating administration ≤ 49 days of amenorrhea. [redacted]

The Division expressed concerns regarding the adequacy of the French data. It was recommended that the Population Council review the data to determine if they meet FDA requirements for adequate and well controlled clinical trials to support the proposed indication. Also, the data as presented suggested a difference in the study designs of the 2 French studies [redacted] The Division recommended that the U.S. study replicate the completed French study, since the treatment regimen reflects the proposed U.S. regimen, 600 mg RU-486 (mifepristone) and 400 mcg Cytotec (misoprostol). The data from the ongoing French study and any other studies of RU-486 usage should be submitted as safety data.

[redacted] indicated that the U.S. pivotal trial could be divided into 2 identical trials provided that any division was made prospectively. [redacted] indicated that the [redacted] amenorrhea would require 2 pivotal trials, therefore, dividing the U.S. protocol into 2 trials with 300 subjects per arm per study should be adequate for both the

initial NDA filing with labeling for ≤ 49 days amenorrhea [redacted]

[redacted] asked about the proposed distribution of RU-486, given the restrictive distribution of the product in the U.K. and France and the availability of government approved abortion clinics in those countries. [redacted] also asked whether data would be collected to support use under less restrictive conditions in this country. [redacted] indicated that the labeling can only describe what has been studied and should be restricted to those conditions under which the drug has been tested. [redacted] stated that this application would not be submitted for an "accelerated approval," therefore, the data would not be required to justify restrictive distribution (if needed, however, the data could be provided to support restrictive distribution/labeling). [redacted]

The Population Council explained that the clinical investigation will be restricted to those physicians with:

1. Experience in performing abortions.
2. Access to an on-site IRB.
3. Access to emergency medical care (e.g., surgical abortion facility and blood transfusions).

[redacted]

[redacted] indicated that the information submitted in a desk copy by Roussel Uclaf provided only the last 4 steps of the drug substance synthesis. The information will be acceptable for the initial submission of the IND but the complete synthesis will be needed for the NDA. Because the starting material is a [redacted], the complete information of its manufacture and controls will be needed to ensure that the product can be replicated by the licensed manufacturer. The IND should be amended to include the synthesis information on the intermediate product.

The Population Council indicated that Roussel Uclaf has submitted new toxicology data. [redacted] requested that the teratology and mutagenicity data be submitted to the IND.

[redacted] recommended that the Population Council use the rate of events with surgical abortions at each study site for comparison to the mifepristone/misoprostol regimen's rate at each site. He also suggested that the Population Council consider the effect weight may have on the effectiveness of the treatment.

The Population Council has tentatively scheduled an investigator's meeting for September 1993. Prior to that meeting they plan to write the clinical protocol, select investigators/clinics, and amend the IND. The NDA is scheduled for submission in 1994.

Actions:

1. The Population Council will amend their IND ——— with the proposed U.S. protocol, an updated Investigator's Brochure, and updated CMC and toxicology sections. The CMC and toxicology will be submitted prior to the clinical section (with desk copies).

2. The U.S. clinical protocol will be prospectively stratified by duration of amenorrhea and divided into 2 identical pivotal trials.

3. The clinical protocol will include hemoglobin and/or hematocrit measurements and Rh typing (with treatment, if necessary) at the initial clinical examination.

/S/

CSO

cc: IND Arch
HFD-510
Attendees
HF-40/ ———
HFD-510/ ———
HFD-511/ ——— '7/20/93/ ——— 'ft/ '8/10/93
concurrence: ——— /7/21/l ——— /7/22/ ——— /7/23/
——— /7/26/ ——— /8/2/93

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

e Population Council
er for
nedical Research

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Telex: 238274 POBI UR

Noted
7/10/92
/S/

ORIGINAL

July 6, 1992

Division of Metabolism
and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Dept. of Health and Human Services
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Noted
/S/ N.A.I.
7/15/92

Re: RU 486 (Mifepristone), IND

Dear

In reply to your letter of 22 June 1992, I would like to point out that Roussel UCLAF have authorized the Population Council to allow the Agency to refer to chemistry, manufacturing and control (CMC) information provided by Roussel UCLAF and filed in the IND In addition, the Agency may reference to all non-clinical (animal data) in our IND. This applies to all previous as well as all future investigators, who have permission to cross index to our IND.

Should you have any further questions, please do not hesitate to contact me.

Sincerely yours,

Irving M. Spitz, M.D.
Senior Scientist

IMS:ma

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER
☒ N.A.I.

/S/
CSO INITIALS

7/15/92
DATE

Memo to the File

TELEFAX

To: Dr. I. Spitz
Pop. Council

FAX: 212 - 327-7678
PHONE: 212 - 327-8734

From:

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX:
PHONE:

Date: 7-11-94

Pages: 1 [inclusive]

IND

Either blank tablets or tablets with a new embossed design can be used. However, comparative dissolution data (USP method) must be submitted to the IND.

TRANSMISSION REPORT

301-443-3282

TTI NO.
DATE AND TIME
DURATION
MODE
PAGE
RESULT

CC: Arch IND
HFD-510
HFD-510/

MIF 004991

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

May 16, 1994

President & CEO
Roussel Uclaf
102, route de Noisy
93235 Romainville Cedex
France

Ms. Margaret Catley-Carlson
President
Population Council
1 Dag Hammarskjold Plaza
New York, New York 10017

Dear [redacted] and Ms. Catley-Carlson:

This letter concerns the assignment by Roussel Uclaf of U.S. patent rights for mifepristone to The Population Council, Inc. As is discussed below, should the Population Council file, and the Food and Drug Administration (FDA) approve, a new drug application (NDA) for mifepristone for termination of early pregnancy, the FDA will take appropriate measures, in the exercise of its statutory authority, to assist in the dissemination of appropriate information to women and their physicians, and to assist through the NDA-approval process in the creation of a regime for distribution and use that will protect against misuse of the drug.

To this purpose, if FDA approves an NDA for mifepristone, the FDA is committed to the following:

1. FDA will cooperate with the NDA sponsor to advise physicians and women who may consider using mifepristone or who do choose to use it of appropriate information concerning the properties of mifepristone and the need for it to be prescribed and used in strict conformity with the label requirements.

2. FDA has received from the Population Council the document entitled "Distribution, Dispensation and Use Requirements" dated 14 April 1994. Based on the limited information now known to FDA, the agency's view is that this document provides appropriate information concerning the drug and establishes a rigorous and responsible distribution and dispensation system that protects against inappropriate use or misuse. After review of all data in any NDA submitted to FDA by the Population Council, FDA will approve the inclusion of the requirements set forth in this document (although not necessarily

in precisely the same wording) in the label for mifepristone that are justified in the NDA, with two exceptions:

A. the type of requirement now stated in Paragraph (c) would be referred to but not included at comparable length in the label; and

B. because the rights assigned are only for the United States, its territories and possessions, the requirement now stated in Paragraph (f) that a patient be a United States resident would be replaced in the label with a requirement that the patient would agree to stay within reasonable proximity to the treatment site until discharged by her physician pursuant to an approved Treatment Procedure in order to ensure completion of the treatment.

Sincerely,

David A. Kessler, M.D.
Commissioner of Food and Drugs

APPEARS THIS WAY
ON ORIGINAL

cc: Arch IND
HFD-510

The Population Council
Center for
Biomedical Research

ORIGINAL

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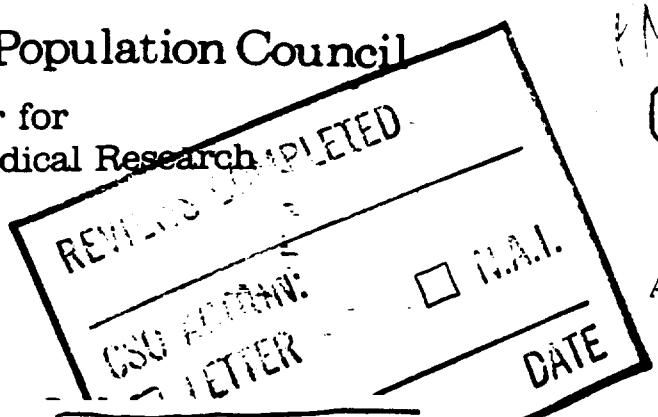

August 3, 1994

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

Re: IND —— (Mifepristone) RU486 Tablets 200 mg
Submission 100 - Protocol and Information Amendment

Dear ——

We refer to our above Investigational New Drug Application (IND) and also to our recent meeting with you on July 7, 1994 to discuss plans for initiation of clinical studies with mifepristone in inducing abortion.

As discussed in that meeting, we are submitting herewith an initial amendment to our IND with is comprised of:

- General investigational plan (estimated project timetable)
- Investigator's brochure
- Protocol and investigator documentation
- Chemistry, manufacturing and control information

The chemistry, manufacturing and control information in this amendment was obtained from the documentation provided earlier by Roussel Uclaf to the Food and Drug Administration and to The Population Council. We anticipate that by September 1, 1994 we will submit a second amendment which will incorporate the remaining preclinical and clinical information in the Roussel documentation into our IND.

Previous submissions to this IND have not utilized a serial numbering system. To initiate the system with this submission, we are designating this submission as number 100 with subsequent submissions to be numbered consecutively in the order in which they are submitted.

In this amendment we propose a pilot study on the use of mifepristone and misoprostol for pregnancy termination in three or four clinics. A total of 15 subjects will be studied in each clinic, giving a total of 45 to 60 subjects who will be treated.

This pilot study is a prelude to a larger phase 3 clinical study which we plan to commence later on in the year to determine the safety, efficacy, acceptability and feasibility of mifepristone and misoprostol for terminating pregnancy in women with amenorrhea of 49 —— days duration. The present proposed pilot study will enable us to assess the feasibility of

the protocol and the adequacy of the case record forms. We wish to commence the pilot study on 15 August and it will be completed by 15 September. Thus the results can be analyzed before a general investigators' meeting which will be scheduled for the beginning of October.

The proposed Protocol No. 166 is enclosed.

This protocol was unanimously approved by the IRB of the Population Council on 29 July 1994, pending the suggested revisions listed below:

1. Cover Page: A signature line for the Principal Investigator(s) should be added.

2. Page 16, 6.7, 1st paragraph: The IRB requested rewording of this paragraph as follows: "Subjects may withdraw from the study at any time."

3. Informed Consent

(a) Page 1: Reword end of first paragraph (third to last sentence) as follows: "The dosage to be studied has been approved for routine use in France for women who are pregnant and have experienced seven weeks amenorrhea or less." "In the latter two countries, it is used in women who are pregnant and with amenorrhea of nine weeks or less." (last sentence in paragraph)

(b) Reword first sentence of second paragraph as follows: "....termination in women who are 63 days or less from the first day of the last menstrual period."

(c) Reword second sentence of second paragraph as follows: ".....in three groups of women who are less than 50 days, 50 through 56 days and 57 through 63 days from the first day of the last menstrual period."

(d) Page 2: Reword the first sentence of first paragraph under "Clinic visits" as follows: ".... a physical examination, *blood test*, and an ultrasound examination ....."

(e) Add to fourth sentence of first paragraph the following: ".... I will return to the clinic (visit 2) *even if I believe I have aborted* and will take ...."

(f) Page 3: Under Risks and discomforts the IRB suggested the addition a statement on the mild discomfort and possible hematoma associated with a blood test.

(g) The second and third paragraphs should be combined and reworded as follows: "I understand that it is not advisable to allow a pregnancy to continue after taking mifepristone and/or misoprostol, since the full effects of mifepristone on the fetus are not known and misoprostol administration in early pregnancy has been associated with abnormal development of the fetus. I understand that abortion after mifepristone/misoprostol is successful in termination of pregnancy in approximately 95% of treated women. When abortion is incomplete, vacuum aspiration or D and C are recommended to terminate bleeding and prevent anemia. ***When abortion does not occur, surgical termination of pregnancy is medically recommended because of the possible risk to the fetus and I have previously agreed to this procedure.***

(h) Page 5: The IRB requested that it should be stated in the Confidentiality section that records are kept in a locked cabinet.

(i) Informed Consent heading: Delete heading; Reword paragraph as follows: "I understand that I may be asked to be interviewed by a representative of the sponsor. The interview will be conducted in the language I speak and will verify that I understand the risks, benefits, proeedures, and the experimental nature of the study. If I do not agree to be interviewed, this will not affect my present or future medical care from the hospital or the clinic, or my participation in the study. I understand that I can change my mind at any time. All information will be kept confidential."

(j) Delete paragraphs under Subject's Statement section and replace with the following: "I, the undersigned, have had the risks and benefits of this study explained to me in my a language that I understand. I agree to participate in this study as a volunteer subject."

(k) Page 6: For signature line of witness, change 'Above Signature' to 'Above Signatures'.

(l) Both Subject's Statement and Investigator's Statement should appear on the same page of the Informed Consent.

Should you have any further queries please don't hesitate to contact me.

Yours very sincerely,

C. Wayne Bardin

C.W. Bardin, M.D
Director

Enclosure

CWB:sw

APPEARS THIS WAY
ON ORIGINAL

Amendment

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*Page number refers to the number stamped in the lower right corner of each page

21 CFR 312.23 (a)(6) – Protocol(s)

(i) A protocol for each planned study.

A copy of Protocol 166 A (Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days) is attached. It is anticipated that pilot studies under this protocol will be initiated at three study centers on August 15, 1994. Following completion of these preliminary three pilot studies and the conduction of an Investigator's Meeting in early October, studies will be initiated at the remaining study centers on October 15, 1994.

Accompanying the protocol is a completed Statement of Investigator (Form FDA 1572) for

Alfred N. Poindexter, III, MD
Baylor College of Medicine
Houston, TX 77030

who will conduct the study at one study center. Information on investigators who will conduct the study at other centers will be forwarded subsequently.

APPEARS THIS WAY
ON ORIGINAL

July 15, 1994

CONFIDENTIAL

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

PROTOCOL NUMBER: 166 A

SPONSOR:

The Population Council
1230 York Avenue
New York, New York 10021

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