IND —— 16 November 1984

Prof. Dept. Reproductive Medicine
——School of Medicine

Submission: 22 October 1984

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

RU 486

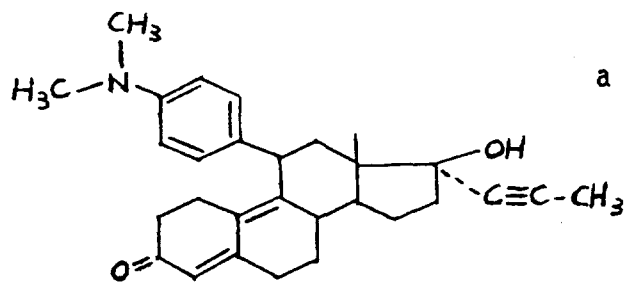
Antiprogestin - Antiglucocorticoid

Intended Use: —— as an early abortifacient

Supplier: Roussel Pharmaceutical

Related: IND —— RU 38486) - abortifacient - The Population Council
(letter of authorization enclosed)
IND ——

Chemical Composition: Synthetic Steroid



a 19-nor steroid
M.W. 429.6

(17β-hydroxy-11β [4-dimethylaminophenyl 1]-17α [prop-1-ynyl]-estra-4,9-diene-3-one)

Proposed Clinical Trial:
Studies are to be separated into four "phases" (so named by the sponsor) or clinical trails. Phase I studies will examine the pharmacokinetics of RU 486 while phases 2, 3 and 4 will examine biological effects and potential clinical applications.

First Phase: To determine half-life and absorption characteristics; 12 normal cycling (non-pregnant) women will be divided into 2 groups of 6 each. One group will receive 4 mg/kg p.o and the second will receive 4 mg/kg i.m. in an ethanol/sesame suspension. Appropriate blood and urine sample analysis and analysis for RU 486 will be made as well as appropriate blood assays for cortisol, estradiol. progesterone, LH, FSH and ACTH.

Second Phase: Biological effects of RU 486 on the menstrual cycle. 40 normal cycling (non-pregnant) women are to be enrolled in a 3 mo. study. Following a 30 days control cycle consisting of assessment of basal hormone secretion, each group of 10 will receive 3 mg/kg RU 486 p.o. for 3 days with treatment cycles being initiated as follows: a) early follicular phase (D1-3); b) late follicular phase (D11-13); c) Midluteal phase (D19-21); d) late luteal phase (D25-27).

This will be followed by a 30 day recovery cycle with blood drawn daily.

Tests will be carried out at various times including endometrial biopsies, pelvic ultrasound for effects on folliculogenesis, and measurements for RU 486, cortisol, ACTH, LH, FSH, E_2 and P_4 (progesterone).

Third Phase: Examination of the ability of RU 486 to interrupt ovarian and endometrial function during simulated early pregnancy. 15 normal cycling women will be divided into 3 treatment groups receiving 1,2 or 3 mg/kg RU 486 p.o. for 3 days beginning on day 19 of the cycle (midluteal). hCG is to be given at a dose of 100 IU/m^2 i.m. beginning on Day 19 and doubled each day thru Day 24 at which time the dose will be 3200 IU/m^2 i.m. (to simulate early pregnancy).

Periodic blood samples will be analyzed for hCG, progesterone, estradiol, RU 486 and cortisol. Endometrial biopsies are to be taken Day 27. Pelvic ultrasound scans are to be used to assess corporus luteum changes.

Studies are to be compared with phase 2.

Fourth Phase: To assess the ability of RU 486 to interrupt early pregnancies between 5-8 weeks of gestation. Seventy women desiring abortion will be divided into 4 treatment groups (20 ea. treated; 10 placebo) receiving 1,2,3 (or placebo) mg/kg/day orally x 3 days. Periodic blood samples will be analyzed for hCG, progesterone, estradiol, RU 486 and cortisol. Pelvic exams or ultrasounds will be done daily. If abortion has not occurred 7 days following RU 486 treatment, vacuum aspiration will be carried out.

Data will be compared with placebo and phase 3 (simulated early pregnancy).

Comments and Conclusions:

This IND for use of RU 486 is essentially similar to IND ——— held by the Population Council. The product RU 486 appears to be identical to that designated RU 38486 for use as an abortifacient under IND ——— [The Population Council ——— IND ———

No preclinical data are submitted in subject IND, however, a summary is submitted which discusses properties and preclinical studies that have been conducted with the drug. A letter of authorization to refer to the Population Council's IND ——— is included.

As discussed in the Pharmacology Summary of IND ——— (dtd. 27 October 1983) by this reviewer, RU 486 is a 19-nor steroid with radicals substituted on C-11 and C-17 related to certain progestagens while reportedly on the other hand related to the total structure of anti-estrogens of the triphenyl series.

Preclinical studies have shown RU 486 to have an affinity for the rabbit progesterone receptor about 5 times that of progesterone, and for the rat thymus glucocorticoid receptor about 3 times that of dexamethasone.

Affinity for the androgen receptor is weak and that for estrogen and mineralocorticoid receptors only negligible. There is a strong anti-progesterone effect with an absence of progesterone activity. RU 486 has an abortive effect in rats with termination of pregnancy apparently due to its anti-progesterone activity exercised at the receptor level. It also appears to be a luteal phase interrupter and abortifacient in monkeys [referenced (IND —— to literature abstract - Healy, Boulieu, Hodgen, Soc. for Gyn. Invest., Wash., D.C., 1983].

The drug has strong anti-glucocorticosteroid activity without agonistic effects. At doses tested, there were no estrogen or anti-estrogen activities or mineralocorticosteroid or anti-mineralocorticosteroid effects per se.

RU 486 is relatively non-toxic acutely in rats, and 30-days studies in rats at doses up to 200 mg/kg and in cynomolgus monkeys at doses up to 100 mg/kg/day in general showed no unexpected toxic effects although three monkeys had to be sacrificed early. Effects seen were essentially those attributable to anti-glucocorticosteroid action. Although some sporadic changes in urinary electrolytes were noted, individual values were in general within range of controls. The findings of perilobular degeneration, thyroid hyperactivity, atrophy of the epithelium of seminal vesicles and prostate, mammary secretions, and persistent estrus with the presence of ovarian follicular cysts in some rats, mainly at higher doses, appeared to be drug related, however, such a relationship was not evident in the monkey study.

Under this IND, the potential benefits utilizing the drug's anti-progesterone activity, appear to be as a —— as an abortifacient by inducing interruption of early pregnancy.

Tablet size and composition are not given. Tablet size under IND —— however, is ——

No preclinical toxicity studies are presented for the — form of the drug in this IND or IND —— Preclinical pharmacology studies have been carried out (IND —— by the i.p., s.c. and i.v. routes and no deaths were produced in male mice at 800 mg/kg i.p. A very low dose pharmacokinetic study has been reported in humans by the i.v. route.

Doses of RU 486 to be used in the proposed clinical trials are in the range of those seen in the literature and the maximum dosage to be utilized is considerably below that which produced signs of adrenal insufficiency in the preclinical studies.

/S/

cc:
Original IND ——
HFN-345; HFN-810 IND ——
HFN-810 Pharmacology; HFN-810 ——

/S/

RU-486 Single-Patient IND Requests

INFORMATION TO BE SUBMITTED TO THE FDA

Provide an introductory letter to the FDA accompanied with the following required information:

1. History of patient including disease status, prior therapy and response and rationale for this treatment.

2. A statement that informed consent and IRB approval will be obtained prior to initiating drug treatment.

3. A signed treatment agreement (see additional pages) or a protocol or a journal article detailing the treatment plan (dose, route, duration), monitoring procedures and modifications for toxicity.

4. FAX from Feminist Majority Foundation indicating that they are willing to provide the drug for single-patient use or send this as soon as you receive it.

5. Completed and signed Form 1571 (blank forms attached).

6. A statement of the investigator's qualifications (first 2 pages of C.V. is acceptable--indicates board certification in neurology or oncology).

7. The protocol or journal article or treatment agreement (signed and dated, with the appropriate information included).

Fax all information to the FDA to the attention of _____ f you have any further questions, please call _____ If your request is approved, an IND number will be issued within 24-48 hours after we receive all the necessary documentation.

OBTAINING DRUG SUPPLY

Also contact _____ at the Feminist Majority Foundation (FMF) to obtain written confirmation of the commitment to supply the drug for single-patient use at the following number:

Phone: 703-841-0540 and FAX: 703-522-2219

FMF may have an additional request for information that you must satisfy.

The FMF will provide a Letter of Authorization (LOA) allowing the FDA to reference the appropriate documentation (IND, DMF) on your behalf as the sponsor of the single patient IND.

Please be Aware of Your Reponsibility as a Sponsor of an IND

As sponsor of this IND, you are responsible to submit the following to your IND: (1) any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information (21 CFR 312.32(c)(2)); (2) any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information (21 CFR 312.32(c)(1)); and (3) annual progress reports (21 CFR 312.33).

Re: Single Patient Use IND for RU-486

Dear Physician:

In order to obtain an Emergency Investigational New Drug (IND) application number for the use of mifepristone in an individual patient, the FDA must have documentation regarding the proposed treatment plan, including the dose, route, duration, monitoring procedures and modifications for toxicity. **In the absence of this information from your initial request, you must agree to treat your patient according to the following treatment plan**. If the treatment plan is modified, the modifications as well as the reasons for modification should be forwarded to the FDA for approval prior to initiation of treatment.

Please provide the information requested below. Your signature indicates your agreement to treat the patient as detailed in the treatment plan.

A copy of this agreement should be maintained in your IND files. A copy of this agreement should also be sent to the FDA via FAX as noted in our previous instructions. The original copy of this agreement, as well as your original request, should be submitted to the FDA upon receipt of correspondence issuing your IND number, including your original, signed FDA Form 1571 (IND application form). This and all other future communications regarding this IND should be forwarded in triplicate, identified with your *IND #* and addressed as follows:

U.S. Postal Service	*By Courier Service*
Division of Oncology Drug Products HFD-150 CDER/FDA 5600 Fishers Lane Rockville, MD 20857	Division of Oncology Drug Products HFD-150 CDER/FDA 1451 Rockville Pike Rockville, MD 20852

If you have any questions, regarding this procedure, please contact _____

Sponsor's Signature: _____ Date: _____
(Your signature indicates your agreement to treat the patient as detailed in the following treatment plan.)

RU 486 Treatment Plan

PLEASE PRINT CLEARLY

IND Sponsor (treating physician): _____

Indication: _____ **Patient's Initials:** _____

Drug: Mifepristone (RU-486)

Dose: 200 mg per day

Route: P.O.

Duration: As Follows: _____

Disease progression, unacceptable toxicity, interruption of therapy for greater than 2 weeks . If study medication is stopped for any reason during the study period, therapy may be reinstituted if the discontinuance does not exceed 2 consecutive weeks or a total of 5 weeks.

Continuation of Therapy:

Patients who are stable or responding to study therapy after 2 years may continue on therapy.

Follow-up of Patients on extended therapy:

Patients who continue their original therapy past 2 years will continue to follow the schedule of clinic visits and studies.

If therapy is stopped for any reason, therapy may be reinstituted if the discontinuance does not exceed 2 consecutive weeks or a total of 4 weeks in any one year.

Toxicities to be Monitored: At each clinic visit, all patients should be specifically questioned concerning:

1. Fatigue
2. Hot Flashes
3. Gynecomastia
4. Hair Loss
5. Cessation/change in menses (Endometrial hyperplasia has been reported.)
6. phlebitis
7. rash
8. dizziness
9. nausea
10. somnolence

If severe adrenal insufficiency is suspected (severe asthenia/SWOG Grade 3-4 weakness) a blood sample for cortisol (preferably AM cortisol) will be immediately collected and assayed. Treatment with hydrocortisone, 25 mg, P.O., three times a day will be initiated. If symptoms do not rapidly improve and if no other cause for asthenia can be found, treatment will be discontinued.

If severe hypothyroidism (SWOG Grade 3-4) is suspected, a blood sample for thyroid function tests will be immediately collected and assayed. Treatment with synthroid, 0.1 mg, P.O. daily, will be initiated. If symptoms do not improve, treatment will be discontinued.

Safety Monitoring Procedures: The following studies are required prior to treatment initiation, and every two (2) to four (4) months, or as necessary, during treatment.

PHYSICAL STUDIES	LABORATORY STUDIES
History	CBC / Differential / Platelets
Physical Examination	Cl- / PO_4
Toxicity Notation	Na+/ K+
Endometrial Biopsy*	Creatinine
	BUN
	Fasting Blood Glucose
	Alkaline Phosphatase✖
	Bilirubin✖
	SGOT✖
	AM cortisol #
	T4, T3, TSH #
	T3 resin uptake #

*We recommend this procedure be performed once every year, or once every 18 months in pre-menopausal women.

✖These studies should be performed every 3-4 months.

These studies should be performed once per year or as clinically indicated (see above comments).

Submitting a Request to Charge for the Investigational New Drug Mifepristone

The following information is provided to aid the licensed medical practitioner in submitting to the FDA a request to charge their patient(s) for the unapproved new drug mifepristone for use under an Investigational New Drug (IND) application.

Usually, the best way for a patient to be treated with an investigational drug is by being enrolled into a formal study sponsored by the drug's commercial sponsor/manufacturer. However, when there is no open clinical trial for which the patient is eligible and has access, the patient's medical practitioner may seek to obtain the drug from a pharmaceutical supplier and submit his/her own IND to the FDA. The practitioner is then the sponsor of the IND and is referred to in this document as the "physician-sponsor." The pharmaceutical supplier may charge the physician-sponsor for the drug. Consequently, the physician-sponsor may wish to recover the costs he/she incurred in obtaining the drug. Under the FDA's regulations 21 CFR 312.7(d), sponsors may not charge patients for investigational drugs except when charging is specifically authorized by the FDA. Normally, the cost of an unapproved drug is presumed to be a routine business cost of drug development. However, in certain situations, upon FDA authorization, costs associated with the manufacture, research and development, and handling of the drug may be passed on to the patient. Permission to charge will only be granted for indications for which there are data showing the activity of mifepristone against the patient's specific disease or condition.

To receive permission to recover his/her cost for the investigational drug, the physician-sponsor must submit to FDA a specific, written request to charge. This and all other communications regarding this IND should be forwarded in triplicate, identified with your *IND #* and addressed as follows:

U.S. Postal Service

Division of Oncology Drug Products
HFD-150
CDER/FDA
5600 Fishers Lane
Rockville, MD 20857

By Courier Service

Division of Oncology Drug Products
HFD-150
CDER/FDA
1451 Rockville Pike
Rockville, MD 20852

The patient may not be charged until written authorization to charge is received from the FDA. If authorization to charge is granted, it will be for a maximum period of one year. If use of the drug is long-term, the physician-sponsor must request renewal of permission to charge in his/her annual report to the IND, which is due to the FDA within 60 days of the anniversary of the date the IND went into effect (usually 30 days after the original IND was received by the FDA; for single-patient INDs, the effective date is the date the IND number was granted).

The request to charge may be included in the original IND application and must contain the following information. If the request to charge is submitted as an amendment to an existing IND, the amendment should include all of the following information not already submitted to the IND as well as a report on the patient's clinical progress on RU-486 (mifepristone).

1. A completed form FDA 1571 (the third block in the shaded region, "CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)" should be checked.

2. A statement as to why the physician-sponsor was not permitted to be included as an investigator under an existing IND, or was not permitted to enroll his/her patient in an ongoing trial.

3. The amount to be charged per unit dose and per month and an explanation of how that amount was determined (physician-sponsors may recover only their cost for the drug). A copy of the bill from the drug supplier should be provided.

Electronic Mail Message

Date: 9/18/00 6:05:13 PM
From: [redacted] ([redacted])
To: [redacted]
Cc:
Subject: R486

Would you email [redacted] a copy of the RU486 package you send out to physicians requesting [redacted] is working with [redacted] to develop a Q & A?
Thanks

/S/
9/28/00

RU-486 (mifepristone)
Single-Patient IND Submission Checklist

Physician Name: _____ Date of Fax: _____

Patient Name/Initials: _____ Indication: _____

YES	NO		ITEM	NOTES
___	___	1.	Patient History	
___	___	2.	Statement re: Informed Consent & IRB approval	
___	___	3.	Protocol, Journal Article or Treatment Agreement	
___	___	4.	FAX commitment from supplier to provide drug	
___	___	5.	Physician/Sponsor CV	
___	___	6.	LOA from the Population Council (not needed to issue IND #)	

If physician intends to charge patient for the drug, the following should be provided:

YES	NO		ITEM	NOTES
___	___	1.	FDA Form 1571 w/ Request to Charge box checked	
___	___	2.	Statement re: exclusion from existing IND or ongoing trial.	
___	___	3.	--amount to be charged/unit dose/month	
___	___		--explanation of how amt was determined	
___	___		--copy of bill from drug supplier	

ROUTED TO:

___ _____

___ _____

Request: Signature

❒ Approved _____

❒ Denied _____

IND Number: _____

Date Issued: _____

Spoke With: _____

Initials: _____

Submitting a Request to Charge for the Investigational New Drug Mifepristone

The following information is provided to aid the licensed medical practitioner in submitting to the FDA a request to charge their patient(s) for the unapproved new drug mifepristone for use under an Investigational New Drug (IND) application.

Usually, the best way for a patient to be treated with an investigational drug is by being enrolled into a formal study sponsored by the drug's commercial sponsor/manufacturer. However, when there is no open clinical trial for which the patient is eligible and has access, the patient's medical practitioner may seek to obtain the drug from a pharmaceutical supplier and submit his/her own IND to the FDA. The practitioner is then the sponsor of the IND and is referred to in this document as the "physician-sponsor." The pharmaceutical supplier may charge the physician-sponsor for the drug. Consequently, the physician-sponsor may wish to recover the costs he/she incurred in obtaining the drug. Under the FDA's regulations 21 CFR 312.7(d), sponsors may not charge patients for investigational drugs except when charging is specifically authorized by the FDA. Normally, the cost of an unapproved drug is presumed to be a routine business cost of drug development. However, in certain situations, upon FDA authorization, costs associated with the manufacture, research and development, and handling of the drug may be passed on to the patient. Permission to charge will only be granted for indications for which there are data showing the activity of mifepristone against the patient's specific disease or condition.

To receive permission to recover his/her cost for the investigational drug, the physician-sponsor must submit to FDA a specific, written request to charge. **The patient may not be charged until written authorization to charge is received from the FDA**. If authorization to charge is granted, it will be for a maximum period of one year. If use of the drug is long-term, the physician-sponsor must request renewal of permission to charge in his/her annual report to the IND, which is due to the FDA within 60 days of the anniversary of the date the IND went into effect (usually 30 days after the original IND was received by the FDA; for single-patient IND's, the effective date is the date the IND number was granted).

The request to charge may be included in the original IND application and must contain the following information. If the request to charge is submitted as an amendment to an existing IND, the amendment should include all of the following information not already submitted to the IND as well as a report on the patient's clinical progress on RU-486 (mifepristone).

1. A completed form FDA 1571 (the third block in the shaded region, "CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)" should be checked.

2. A statement as to why the physician-sponsor was not permitted to be included as an investigator under an existing IND, or was not permitted to enroll his/her patient in an ongoing trial.

The amount to be charged per unit dose and per month and an explanation of how that amount was determined (physician-sponsors may recover only their cost for the drug). A copy of the bill from the drug supplier should be provided.

APPEARS THIS WAY
ON ORIGINAL

RENEWAL of RU-486 Single-Patient IND Requests

If you wish to obtain RU-486 (*mifepristone*) for a patient who was previously treated with the product, please follow these procedures:

1. **OBTAINING DRUG SUPPLY**
   Contact it the Feminist Majority Foundation (FMF) at one of the following numbers:

   Phone: **FAX:**

2. **INFORMATION TO BE SUBMITTED TO THE FMF**

   a. IND number.

   b. Date IND number was issued.

   c. IND Physician/Sponsor name.

   d. Patients Initials.

   e. Indication.

3. **CHARGING PATIENTS**
   If the physician intends to charge the patient for the supply of RU-486 [redacted] per tablet), please read the attached document titled "Submitting a Request to Charge for the Investigational New Drug Mifepristone" and submit the required information to the Food & Drug Administration (FDA).

4. **REQUESTING AN INVESTIGATIONAL NEW DRUG (IND) APPLICATION NUMBER**
   Send all information required in item #3, **via facsimile**, to the attention of [redacted]

NOTE: The timeframe for approval of your request to charge for the drug is approximately 2 months. However, the drug supply may be distributed to the patient prior to the approval of a request to charge. **Under no circumstances can a physician/sponsor charge a patient for an investigational drug until written authorization to charge is received from the FDA** [21 CFR 312.7(d)].

QUESTIONS?? Call [redacted] **(direct line).**

APPEARS THIS WAY
ON ORIGINAL

RU-486 Single-Patient IND Requests

1. **OBTAINING DRUG SUPPLY**
   Contact at the Feminist Majority Foundation (FMF) at one of the following numbers:

   Phone: **FAX:**

   to obtain: written confirmation of their commitment to supply the drug for single-patient use.

   NOTE: FMF will provide a Letter of Authorization (LOA) allowing the FDA to reference the appropriate documentation (IND, DMF) on behalf of the physician/IND sponsor.

2. **INFORMATION TO BE SUBMITTED TO THE FDA**

After receiving FMF=s FAX, **provide** the following information in a letter to the FDA with the following attachments:

   a. **History of patient** including disease status, prior therapy and response and rationale for this treatment.

   b. A statement that **informed consent** and **IRB approval** will be obtained prior to initiating drug treatment.

   c. A signed **treatment agreement** (see additional pages) or a **protocol** or a **journal article** detailing the treatment plan (dose, route, duration), monitoring procedures and modifications for toxicity.

   d. Attachments:

      (i) **FAX from FMF** indicating that they are willing to provide the drug for single-patient use.

      (ii) Statement of the **investigator's qualifications** (first 2 pages of C.V. is acceptable--indicates board certification in neurology or oncology)

      (iii) **Protocol** or **journal article** or **treatment agreement** (signed and dated, with the appropriate information included).

3. **CHARGING PATIENTS**

If the physician intends to charge the patient for the supply of RU-486 ($5.00 per tablet), please read the attached document titled "Submitting a Request to Charge for the Investigational New Drug Mifepristone" and submit the required information.

4. **REQUESTING AN INVESTIGATIONAL NEW DRUG (IND) APPLICATION NUMBER**

Send all information noted in #2 plus attachments, and #3, if appropriate, **via facsimile** to the attention of _____

If your request is approved, an IND number will be issued within 24-48 hours after we receive all the necessary documentation.

QUESTIONS?? Call _____ (direct line).

RE: Single Patient Use IND for RU-486

Dear Physician:

In order to obtain an Emergency Investigational New Drug (IND) application number for the use of mifepristone in an individual patient, the FDA must have documentation regarding the proposed treatment plan, including the dose, route, duration, monitoring procedures and modifications for toxicity. In the absence of this information from your initial request, you must agree to treat your patient according to the following treatment plan. If the treatment plan is modified, the modifications as well as the reasons for modification should be forwarded to the FDA for approval prior to initiation of treatment.

Please provide the information requested below. Your signature indicates your agreement to treat the patient as detailed in the treatment plan.

A copy of this agreement should be maintained in your IND files. **A copy of this agreement should also be sent to the FDA via facsimile to the attention *Project Manager*** The original copy of this agreement, as well as your original request, should be submitted to the FDA upon receipt of correspondence issuing your IND number, which will include an FDA Form 1571 (IND application form).

If you have any questions, regarding this procedure, please contact _____ at _____

Sponsor's Signature: _____

Date: _____

RU 486 Treatment Plan

PLEASE PRINT CLEARLY

IND Sponsor (treating physician): _____

Indication: _____ Patient's Initials: _____

Drug: Mifepristone (RU-486)

Dose: 200 mg per day

Route: P.O.

Duration: Disease progression, unacceptable toxicity, interruption of therapy for

Duration: Disease progression, unacceptable toxicity, interruption of therapy for greater than 2 weeks

If study medication is stopped for any reason during the study period, therapy may be reinstituted if the discontinuance does not exceed 2 consecutive weeks or a total of 5 weeks.

Continuation of Therapy:

Patients who are stable or responding to study therapy after 2 years may continue on therapy.

Follow-up of Patients on extended therapy:

Patients who continue their original therapy past 2 years will continue to follow the schedule of clinic visits and studies.

If therapy is stopped for any reason, therapy may be reinstituted if the discontinuance does not exceed 2 consecutive weeks or a total of 4 weeks in any one year.

Toxicities to be Monitored: At every clinic visit, all patients, should be specifically questioned concerning:

1. Fatigue
2. Hot Flashes
3. Gynecomastia
4. Hair Loss
5. Cessation/change in menses (Endometrial hyperplasia has been reported.)
6. phlebitis
7. rash
8. dizziness
9. nausea
10. somnolence

If severe adrenal insufficiency is suspected (severe asthenia/SWOG Grade 3-4 weakness) a blood sample for cortisol (preferably AM cortisol) will be immediately collected and assayed. Treatment with hydrocortisone, 25 mg, P.O., three times a day will be initiated. If symptoms do not rapidly improve and if no other cause for asthenia can be found, treatment will be discontinued.

If severe hypothyroidism (SWOG Grade 3-4) is suspected, a blood sample for thyroid function tests will be immediately collected and assayed. Treatment with synthroid, 0.1 mg, P.O. daily, will be initiated. If symptoms do not improve, treatment will be discontinued.

Safety Monitoring Procedures: The following studies are required prior to treatment initiation, and every two (2) to four (4) months, or as necessary, during treatment.

PHYSICAL STUDIES LABORATORY STUDIES

Date

ROUTING AND TRANSMITTAL SLIP

TO: *(Name, office symbol, room number, building, Agency/Post)*	Initials	Date
1.		
2.		
3.		
4.		
5.		

	Action		File		Note and Return
	Approval		For Clearance		Per Conversation
	As Requested		For Correction		Prepare Reply
	Circulate		For Your Information		See Me
	Comment		Investigate		Signature
	Coordination		Justify		

REMARKS

Please call ——
and convey ——
concerns.

/S/

DO NOT use this form as a RECORD of approvals, concurrences, disposals, clearances, and similar actions

FROM: *(Name, org. symbol, Agency/Post)*	Room No.—Bldg.
	Phone No.

5041-102
☆ U.S.G.P.O.: 1993 342-198/80007

OPTIONAL FORM 41 (Rev. 7-76)
Prescribed by GSA
FPMR (41 CFR) 101-11.206

MIF 008723

RE: Single Patient Use IND for RU-486

Dear Physician:

In order to obtain an Emergency Investigational New Drug (IND) application number for the use of mifepristone in an individual patient, the FDA must have documentation regarding the proposed treatment plan, including the dose, route, duration, monitoring procedures and modifications for toxicity. In the absence of this information from your initial request, you must agree to treat your patient according to the following treatment plan. If the treatment plan is modified, the modifications as well as the reasons for modification should be forwarded to the FDA for approval prior to initiation of treatment.

Please provide the information requested below. Your signature indicates your agreement to treat the patient as detailed in the treatment plan.

A copy of this agreement should be maintained in your IND files. **A copy of this agreement should also be sent to the FDA via facsimile to the attention of ——— ——— Project Manager at ———** The original copy of this agreement, as well as your original request, should be submitted to the FDA upon receipt of correspondence issuing your IND number, which will include an FDA Form 1571 (IND application form).

If you have any questions, regarding this procedure, please contact ——— at ———

Sponsor's Signature: _____

Date: _____

RU 486 Treatment Plan

PLEASE PRINT CLEARLY

IND Sponsor (treating physician): _____

Indication: _____ Patient's Initials: _____

NOTICE OF FORTHCOMING MEETING

Subject: IND —— Population Council

Drug: Mifepristone

Date: October 24, 1995

Time: 9:00

Place: C/R 'N'

Purpose:
Pre-NDA meeting to discuss the sponsors filing plans.

Attendees:

[redacted]

If Interested:

[redacted]

meeting set up by ——10.2.95

APPEARS THIS WAY
ON ORIGINAL

10/24/91
9:00
c/R -N

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

Attending for The Population Council:

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

Proposed Agenda

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

IND [redacted]

Mifepristone Tablets, 200 mg

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

The Population Council
New York, NY 10021

TABLE OF CONTENTS

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popbiomed, New York
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Telex: 238274 POBI UR

September 8, 1994

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

Subject: IND [redacted] Mifepristone Tablets, 200 mg
Submission Serial Number: 103
Information Amendment: Pharmacology/Toxicology/Clinical

Dear [redacted]

We refer to our above Investigational New Drug Application (IND) and also to our 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, to support our proposed studies with mifepristone, we wish to incorporate into this IND the portfolio of information provided earlier by Roussel Uclaf to the Food and Drug Administration and to The Population Council. Our amendment of August 3, 1994 (Submission Serial Number 100) included the chemistry, manufacturing and controls information provided by Roussel and this submission includes the preclinical and clinical information in the portfolio. The information has been reorganized into a format more typical of an IND submission.

Please advise me of any questions or comments regarding this submission.

Sincerely yours,

Attachment

29-35 Mailed Clin

NOV 30 1995

Pre-NDA
Mifepristone

Population Council
October 24, 1995

Memorandum of Meeting

Industry Participants:

Ann Robins, Ph.D., Staff Scientist, Population Council

FDA Staff:

[(HFD-713)

(HFD-426)]

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

Discussion and Conclusion:

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

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

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

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

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

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

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

Action Items:

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

/S/

———, CSO

cc:
IND ———
HFD-510
MEETING ATTENDEES
HFD ———
HFD ———
HFD-510/ ———
HFD-510/ ——— 10.25.95/pop.pnd
concurrences: ——— 10.26.95/ ——— 10.26.95/ ——— 10.27.95/ ——— 10.31.95/ ———
11.1.95/ ——— 11.1.95/ ——— 11.2.95/ ——— 11.2.95/ ———
11.6.95/ ——— 11.16.95

MEETING MINUTES

IND —

27 October 1983

The Population Council

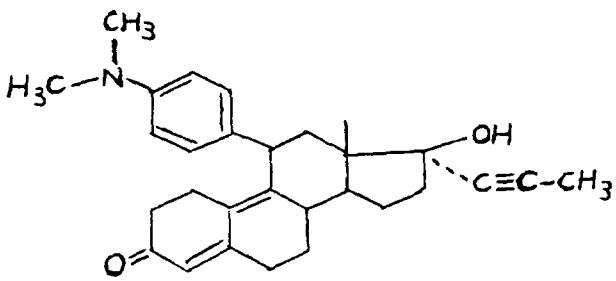
Submission: 3 May 1983

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

RU 38486

Antiprogestin - Antiglucocorticoid
Intended clinical usage: ——— as early abortifacient.
Related: IND ———

Structural Formula: (oral 50 mg tablets)



a 19-nor steroid
M.W. 429.6

17β-Hydroxy-11β-(4-dimethylaminophenyl)-17α-(prop-1-ynyl)-estra-4,9-dien-3-one
Synthesized by the Centre de Recherches Roussel UCLAF (France)

B. Study II: Tolerance Study in Healthy Women. The aim of the study is to investigate the tolerance of RU 38486 adm. orally and its ability to change steroid hormone patterns when given as a single dose to healthy female volunteers (age18-40 yrs.) in the mid-luteal phase (5-9 days post ovulation). Four volunteers will be needed for each of 4 doses (50, 100, 200 and 400 mg). Each volunteer will undertake adequate mechanical contraceptive measures or will be surgically sterilized.

Preclinical Studies:

RU 38486 - Antiprogesterone Activity - Roussel UCLAF, Report AL/23. D. Philibert and C. Tournemine. 9 Dec. 1981.

In vitro - Binding with cytoplasmic receptors of steroid hormones - For progesterone receptors - 5 times that of progesterone and for glucocorticoid receptors - 3 times that of dexamethasone; moderate for androgen receptors and negligible for estrogen and mineralo-corticoid receptors.

In vivo - Oral - Antiprogesterone activity: 50 mg/kg did not show any progestomimetic activity in the Clauberg test.

5 mg/kg inhibits 50% of the action of 0.2 mg/kg progesterone. 20 mg/kg produced complete inhibition.

5 mg/kg RU 38486 totally inhibited maintenance of gestation by progesterone or RU 5020 (?) in the castrate rat on day 8 of gestation. A dose of 10 or 40 mg/kg totally inhibits any increase in LH caused by 4 mg/kg of progesterone in castrated rats pretreated with estradiol.

20 mg/kg in gestating rats is anti-implantatory and abortative no matter what period it is administered.

Preliminary trials in mice also show it to be abortive with an ED_{50} of ca. 2 mg/kg.

Up to a dose of 100 mg/kg, RU 38486 does not show any of the following activities: uterotropic activity in mice and above 100 mg/kg in rats only a slight uterotrophy. Allen-Doisey test (keratinization of vaginal cells in castrated rats) and the Clauberg test (proliferation of endometrium of rabbits pretreated with estradiol) in which it does not induce a progesterone response. Androgen activity in castrated rats:- There is no increase in the weight of prostate, seminal vesicles or levator ani. - Glucocorticoid activity in rats: - No anti-inflammatory activity was produced in the cotton granuloma tests and no thymolytic effect.

A strong anti-glucocorticoid activity which corresponds to its strong affinity for the glucocorticoid receptor is present in rats.

10 mg/kg shows a moderate anti-androgen activity on the weight of the seminal vesicles and on the prostate at 30 mg/kg. 100 mg/kg produced a very weak anti-estrogen activity in immature rats.

Pharmacological and Toxicological Studies of RU 38486: Roussel UCLAF Report AK/17 28 April 1981. D. Philibert; J. Benzain; M. Fortin; C. Tournemine; R. Deraedt.

EOPS - Sprague-Dawley rats and EOPS Swiss mice. Drug adm. in aqueous dispersion of carboxy methylcelluose (0.25%) and polysorbate 80 (0.20%).

RU 38486 shows an affinity for the glucocorticoid receptor (rat thymus) about 3-times that of dexamethasone and 30-100 times that of cortexolone. This affinity does not change as a function of time of incubation. The affinity for progesterone receptors (rabbit uterus) increases in the course of incubation to 5-times that of progesterone.

Androgen receptor (rat prostate) affinity is weak and that for mineralocorticoid (rat kidney) and estrogen receptors (mouse uterus) is negligible.

Rat thymocytes - uridine incorporation: The effect of dexamethasone inhibition of uridine incorporation was practically maximum beginning at 10^{-7}M. No glucocorticoid activity was seen with RU 38486 and cortexolone up to a conc. of 10^{-6}M.

Antiglucocorticoid activity - $5x10^{-8}$M RU 38486 inhibits by 50% the effect of $5x10^{-8}$M dexamethasone on uridine incorporation; $5x10^{-6}$M caused total inhibition. A much weaker antiglucocorticoid activity was seen with cortexolone - 50% inhibition was not exceeded at 10^{-6}M.

Induction of tyrosine aminotransferase (TAT) in rat hepatoma cells (HTC). Dexamethasone causes maximum induction starting at a conc. of 10^{-7}M; no effect was observed with RU 38486 at 10^{-5}M. RU 38486 inhibits more than 80% of TAT induction caused by an equivalent concentration of dexamethasone. Total inhibition is caused by 10^{-6}M no matter what the concentration of dexamethasone.

0.01 mg/kg dexamethasone causes induction of tryptophan pyrolase (TP) and TAT in adrenalectomized rats, and compared to control, a 6-10 fold increase in glycogen. Values for the same dose were doubled in normal rats.

Both orally and i.p., RU 38486, beginning at 5 mg/kg antagonized more than 50% of the effect of dexamethasone on TP in adrenalectomized rats. Orally antiglucocorticoid action is seen by inhibition of effects of dexamethasone at the level of TAT (-50%) and glycogen (-100%). No inhibitory activity was noted with RU 38486 alone at 100 mg/kg i.p. or 50 mg/kg p.o.

In normal rats, RU 38486 totally opposes effects of dexamethasone on TP and TAT beginning at 10 mg/kg p.o. When given alone TP values are lower than controls. Cortexolone, 100 mg/kg p.o., exhibits no anti-dexamethasone activity on TP or TAT in the normal rat.

Rat Thymus weight effects. - Beginning at 5 mg/kg RU 38486 significantly inhibits the thymolytic effect of dexamethasone. Liver and adrenal weights were also increased at 25 mg/kg. 100 mg/kg cortexolone showed no antiglucocorticoid activity.

Cotton granuloma test - 100 mg/kg RU 38486 p.o. significantly inhibits the anti-inflammatory and thymolytic action of dexamethasone. With regard to body growth, it also antagonizes the catabolizing effect of dexamethasone.

0.05 mg/kg dexamethasone s.c. significantly decreases the corticotropic activity of plasma of the adrenalectomized rat. 10 mg/kg RU 38486 p.o. totally inhibits this effect. 100 mg/kg cortexolone shows no anti-dexamethasone effect.

0.05 mg/kg dexamethasone s.c. causes a significant increase in the volume and potassium content of the urine with a sig. decrease in the Na^+/K^+ ratio in adrenalectomized rats. Beginning with 5 mg/kg, and totally with 10 mg/kg, RU 38486 p.o. inhibits the dexamethasone action on K^+ and the Na^+/K^+ ratio. At 25 mg/kg urine vol., K^+ and especially Na^+ are lower than controls. 10 mg/kg of RU 38486 alone does not show such definite effects.

Urine volume, K^+ and Na^+ are increased without a change in the Na^+/K^+ ratio in normal rats given dexamethasone. 10 mg/kg RU 38486 p.o. totally inhibits these effects. 25 mg/kg RU 38486 with or without dexamethasone leads to urinary K^+ and Na^+ sig. less than those of controls. (urine vol. is decreased following RU 38486 alone.100 mg/kg Cortexolone p.o. shows no antiglucocorticoid activity in normal or adrenalectomized rats.

RU 38486 showed no progestamimetic activity in the Clauberg test with 20 mg p.o. However, this dose totally inhibits the effect of 0.2 mg progesterone.

At 1 mg/rat/day x 8 RU 38486 showed neither an androgen nor an anti-androgenic effect in castrated male rats. 5 mg was poorly tolerated.

RU 38486 showed little or no uterotrophic or anti-estrogenic effects at doses up to 1 mg p.o. in immature female mice. No uterotrophic activity was seen in rats at up to 3 mg.

General Pharmacology:
Roussel UCLAF, Report AM/52 29 July 1982. R. Fournex, J. Fichelle, S. Jouquex

Central Nervous System (10, 30, 100 mg/kg p.o.)

General Behavior in mouse and rat.

Administration of RU 38486 provokes no behavior alteration and only a slight decrease in rectal temperature.

Anticonvulsive effect in the mouse.

Electroshock - RU 38486 does not provoke anticonvulsive effects.

Pentylenetetrazol - RU 38846 does not provoke anticonvulsive effects.

Oxotremorine Antagonism in the mouse.

RU 38486 does not exert any antagonism towards the central or peripheral cholinergic effects of oxotremorine.

Interaction with Reserpine in the mouse.

Reserpine Hypothermia is slightly increased in animals treated 6 hours after treatment.

Interaction with 5-HTP in the mouse.
RU 38486 shows no serotoninergic effect.
Potentiation of Hexobarbital sleeping time in the mouse.
A dose-dependent potentiation of the hypnotic effect was noted in mice treated with RU 38486.

Cardiovascular and Respiratory Systems in the Anesthetized Dog (0.3-1-3 and 10 mg/kg i.v.).
Hemodynamics and Effect on Respiration.
RU 38486 did not provoke significant variations of the parameters recorded. Transient effects were hypotension and hyperpnea at time of injection.
Interaction with Mediators.
The presser effects of adrenaline, noradrenaline, histamine and acetylcholine were hardly altered after injection of RU 38486.

Autonomic Nervous System.
A high concentration of 1×10^{-4}M, RU 38486 exerts a strong antagonism as compared with acetylcholine, histamine and serotonin.
Isolated Guinea Pig Seminal Vesicals.
No adrenolytic effect on seminal vesicals.
Nictitating membrane of the Anesthetized Cat.
RU 38486 exerts no adrenolytic or ganglioplegic effect after i.v. administration (1 to 10 mg/kg).

Analgesic and Anti-inflammatory Effects (10, 30 and 100 mg/kg p.o.).
Acetic Acid-Induced Stretching in the mouse.
RU 38486 shows no analgesic effect.
Hot Plate Test in mice.
No analgesic effect.
Carragheenin Paw Edema in the rat.
No anti-inflammatory effects.

Digestive System in the Rat (10, 30 and 100 mg/kg p.o.)
Gastric Secretion (Shay method).
No alteration of the volume or pH of the gastric secretion was noted.
Gastric Transit
RU 38486 does not alter the gastric transit.
Ulcerogenic Effect
No ulcerogenic effects.
Intestinal Transit
Not altered.

Effect on Diuresis in the Rat.
Administration of RU 38486 provokes a distinct decrease in Na^+ (10, 30 and 100 mg/kg) and K^+ (30 and 100 mg/kg). The ratio Na^+/K^+ is slightly decreased. Water excretion was increased by the high dose.

Effect on Glycemia in the Rat.
A tendency towards hypoglycemia was noted particularly at 30 and 100 mg/kg at 2 hours post-dose.

Effect on Blood Coagulation in the Rat.
RU 38486 does not alter the Quick-time and does not inhibit the anticoagulating effect of warfarin.

Effect on Platelet Aggregation.
At concentrations of 1×10^{-6} and 1×10^{-5}M, RU 38486 has no effect on ADP- or collagen-induced platelet aggregation.

Acute Toxicity: Roussell UCLAF, Report AK/17 (cont'd. from above)

Male mice (7 days obs.) - No deaths at 1000 mg/kg p.o. or 800 mg/kg i.p.
Only slight dyspnea at high doses.

10 Day Toxicity Test in Rats.
Male and Female Rats - 60 mg/kg/day x 10
No sig. variation in ion, protein or serum lipid balances
Organ weight changes (reported as not stat. sig.)
ovaries +61%; uterus -28%; liver +8-12%
male adrenals +40% (sig.)

30 Day Oral Toxicity Study of RU 38486 in the Rat. AL 34 Roussel UCLAF, 17 Dec. 1981.
Signed: L. Audegond; R. Deray; M. Cotard; E. Collas; R. Glomot; M. Mouren
Study Dates: Males - 22 Jun - 23 July 1981; Females - 29 June - 30 July 1981.

Dose: 0, 8, 40, 200 mg/kg/day 7 days/week - 0.25% in an aqueous susp. of sodium carboxymethylcellulose containing 0.20% polysorbate 80. via esophageal probang. Lot No. 5

No. Animals: 10M;10F/dose level EOPS (specific pathogen free) Sprague-Dawley rats age 5 wks.

Results:
Clinical Signs: Behavior - normal. Arterial pressure moderately decreased in male rats at 200 mg/kg.
Mortality: None
Body Weights: Male rats - moderate lag beginning 3rd wk on 200 mg/kg.
Food and Water Consumption: Males - normal food. Females - food increased in low dose during 2nd week. Increase in water consumption - moderate in 200 mg/kg males at end of treatment and all 3 female doses at beginning and end of treatment.
Ophthalmologic Exam: No vascular lesions.
Hematology: In general normal variations except increase in total number of leukocytes and more particularly lymphocytes in 200 mg/kg females.
Coagulation: Platelet count and cephalin-kaolin times were slightly increased in males and females at 40 and 200 mg/kg.
Blood Chemistry: Some variations - in most cases decreases and most remained within normal
Males - decreases in Cl^-; chol.; albumin; alk. phos.
Females - decreases in glu.; albumin; alk. phos. (mid-dose)
M & F - BUN within N but slight increases at 200 mg/kg.
Hormones: No sig. differences noted in mean corticosterone, testosterone and prolactin. Progesterone levels increased in mid and high dose females. Some individual variation
Urinalysis: Na^+ and Cl^- - mod increase in high dose F. Cl^- - male 8 & 40 mg/kg decrease
Fecal Exam: Blood free.

Organ Weights:

Absolute

Increases - Liver - hd M &F; Kidney - mid & hd F; Thyroids - hd (non sig.) M & F; Pituitary - low and mid F; Ovary - mid-dose.

Decreases - Kidney - hd M; Thymus - hd M; Pituitary - hd M; Testicle - low and hd; Seminal ves & prostate - mid & hd; Uterus - dose rel.

Relative

Increases - Liver - dose rel. M & mid and hd F; Kidney - treated F; Spleen - mid M; Thyroid - hd M; Pituitary - low and mid F; Ovaries - low and mid.

Decreases - Prostate - mid & hd; Sem. Ves. - mid & hd; Uterus - mid & hd.

Gross Pathology:

Seminal vesicles atrophied in 2 mid-dose and 4 high dose. Other findings appeared isolated.

Histopathology:

Liver - perilobular fatty degeneration - hd F.

Thyroid - hyperactivity - control, low to high dose 0, 3*, 2, 8 males and 0, 0, 0, 10 females. *one animal - 1 hyperactive and 1 dormant lobe

Adrenals - sl hyperplasia fascicular cells - 2 hd F.

Seminal Vesicles & Prostate - atrophy of epithelium at high dose.

Testicular atrophy lesions with spermatogenesis disorders - 5 low dose males only.

Blockade of estrus (esp. visible at vaginal level) - low, mid, high doses = 9, 10, 9 with follicular cysts in ovaries of 0, 5, 3 and with mammary secretion in 1 control (in estrus), 4 low, 9 mid (1 missing) and 8 high dose.

Male rats had normally developed mammary parenchyma.

Other findings were apparently spontaneous.

30 Day Oral Toxicity Study of RU 38486 in Cynomolgus Monkeys (Macaca fascicularis).

Report RSL 492/81937 dtd. 21 April 1982.

Signed:

Dosing began 11 Aug. 1981.

Dose: 0, 4, 20, 100 mg/kg/day 7 days/week in 1% methylcellulose ~~in~~ water. 4 ml/kg by gastric intubation.

No. Animals: 3M;3F/group age 2-4 yrs. wts. 2.35 to 4.85 kg

Results:

Mortality: 3 high dose (135 ♂; 137 ♂; 140 ♀) killed after ca. 2 wks. (Days 13, 14 & 16) for humane reasons. Signs included: vomiting, diarrhea, reduced appetite, body wt. losses. Pre-terminal blood - raised serum urea and cortisol; increased ESR in 2 and increased Met-Hb in the 3rd. 2 had high creatinine and low chloride.

Adrenals were enlarged and ovaries (ovarian cysts) were enlarged in the female.

Histology - no morphological changes to account for condition.

Survivors:
Clinical Signs: Intermittent diarrhea and fecal blood and mucus in some dosed animals. Occasional vomiting in some.
Vaginal Cytology: (Daily) - No treatment related changes. Prior to start of dosing evidence of menstruation had been seen on one or 2 occasions for 11/12 females (not observed in #130 - 20 mg/kg/day.)
Body Weight: Small wt. losses in 2 surviving hd F. Progressive weight loss seen each week for 133♂ (20 mg/kg) resulting in a total wt. loss of 1100 gms. (due to poor appetite). 3 other 20 mg/kg - small wt. losses during 1st 2 wks. only. Mean body weight gains of treated were less than controls.
Food Consumption: Reduced in some animals at 20 and 100 mg/kg.
Water Consumption: Variable to small reduction for some 20 and 100 mg/kg animals.
Ophthalmoscopic Exams: appeared normal. (pre-terminal not performed on sacrificed animals 135♂ and 140♀.
ECGs: No apparent abnormalities. (Sacrificed monkey 135♂ not examined.)

Hematology: (pre-dosing, during wk.4) Neutrophils varied - increased for 139♂ high dose and 129♂ mid-dose which contributed to total white cell counts - normal on repeat investigation. 121♂ (control) showed reduced PCV, Hb and RBC. These were increased for 128♀ (4 mg/kg) and 129♂ (20 mg/kg). Platelets reduced for 121♂ (control). Normal results 6 days later.
2/3 high dose survivors - slight hypochromasia in one and sl anisocytosis in 2
Biochemical Parameters: (pre-dosing and during wk. 4) Pre-dosing a few individual results were outside normal.
Serum leucine arylamidase (LAP) - increased 1 ea. control, low & mid dose (low & m also pre-dose).
SGPT - increased in same 1 control and low dose(also pre-dose)
Other changes sporadic.
Hormone Levels (day 30): Significantly increased cortisol levels in mid and high dose. Estradiol, progesterone and testosterone - variable with no obvious differences.
Bone Marrow Exam: Normal
Urinalysis: Mean volumes increased for the two higher doses. SpGs low in some control and treated - most normal or near normal on repeat. Mean creatinine (20 mg/kg) Na^+, K^+ and Cl^- (sig.) were greater than controls. Individual values were in general within range of controls.
Fecal Occult Blood: Survivors - negative (Sacrificed-not tested during dosing.)

Organ Weights:
Adrenals - (markedly increased for sacrificed) high dose survivors also sig. increased compared to controls.
Heart and Kidney - High dose increased when compared to body weights - weight loss?

Gross Findings (Survivors): Cervix appeared enlarged in several treated females - normal histologically.
Histology (Survivors):
Adrenals: Increased width and eosinophilia of cells of zona fasciculata M & F mid and high dose.
Other findings appeared to occur with equal frequency in controls or were sporadic.

Quality Assurance - Present

APPEARS THIS WAY
ON ORIGINAL

Preliminary Pharmacokinetic Study of ^{3}H RU 38486 in Humans. Roussel UCLAF
J. Salmon, Ph.D.; I. Jung-Testas, Ph.D.; C. Cousty. 30 July 1982.

^{3}H RU 38486 was tritiated in position 6 and 7 with a specific activity of 37.5 Ci/mmol (87.5 mCi/mg)

Dose: 4 Healthy volunteers (3M;1F) received 12.5 µCi - 140 ng ^{3}H RU 38486 i.v. 1 M 3 wks. after i.v. adm. also received 50 mg (ca. 6 µCi) orally.

Results: After i.v. adm., half-lives of distribution are 0.5 and 0.4 hr. and elimination 10 and 16 hrs. with apparent initial volume of distribution of 7 and 8 liters and at steady state 24 and 12 liters for RU 38486 and total radioactivity (parent product + metabolites). Half-lives of elim. and vol. of distribution are reported as being close to these values after p.o. adm.

Urinary excretion is 10-15% of radioactivity within 60-72 hrs. At least 7 metabolites were detected in plasma (none higher than RU 38486). The percentage of radioactivity which accounts for RU 38486 24 hrs. after adm. is 24% after i.v. and 11% after p.o. adm.

Comments and Conclusions:

RU 38486 is a 19-nor steroid with radicals substituted on C-11 and C-17 related to certain progestagens while reportedly on the other hand related to the total structure of anti-estrogens of the triphenyl series.

Preclinical studies have shown RU 38486 to have an affinity for the rabbit progesterone receptor about 5 times that of progesterone, and for the rat thymus glucocorticoid receptor about 3 times that of dexamethasone.

Affinity for the androgen receptor is weak and that for estrogen and mineralocorticoid receptors only negligible. There is a strong anti-progesterone effect with an absence of progesterone activity. RU 38486 has an abortive effect in rats with termination of pregnancy apparently due to its anti-progesterone activity exercised at the receptor level. It also appears to be a luteal phase interrupter and abortifacient in monkeys (referenced to literature abstract - Healy, Boulieu, Hodgen, Soc. for Gyn. Invest., Wash., D.C., 1983).

The drug has strong anti-glucocorticosteroid activity without agonistic effects. At doses tested, there were no estrogen or anti-estrogen activities or mineralocorticosteroid or anti-mineralocorticosteroid effects per se.

RU 38486 is relatively non-toxic acutely in rats, and 30 day studies in rats at doses up to 200 mg/kg and in cynomolgus monkeys at doses up to 100 mg/kg/day in general showed no unexpected toxic effects although three monkeys had to be sacrificed early. Effects seen were essentially those attributable to anti-glucocorticosteroid action. Although some sporadic changes in urinary electrolytes were noted, individual values were in general within range of controls.
The findings of perilobular degeneration, thyroid hyperactivity, atrophy of the epithelium of seminal vesicles and prostate, mammary secretions, and persistent estrus with the presence of ovarian follicular cysts in some rats, mainly at higher doses, appeared to be drug related, however, such a relationship was not evident in the monkey study.

The ultimate proposed use of RU 38486 under this IND is as an abortifacient utilizing the drug's anti-progesterone activity to terminate pregnancy.

Initially the sponsor proposes to conduct tolerance studies in healthy men and women using doses up to ca. 8 mg/kg. Once the safety of single doses has been established, more detailed short term studies (D & E) are planned at doses up to ca. 4 mg/kg. It has been reported in the literature that daily doses up to 4 mg/kg/day for 4 days and single doses of 6 mg/kg given to normal human subjects produced no toxicity or side effects.

Doses of RU 38486 to be used in the proposed clinical trial are in the range of those seen in the literature and are to increase in a stepwise fashion with the maximum dosage to be utilized being considerably below that which produced signs of adrenal insufficiency in the preclinical studies.

NOTE:
Pages of this submission are not consecutively numbered. This has been previously brought to the sponsor's attention to no avail under other INDs.

/S/

/S/

10/28/83

cc:
Original IND ——
HFN-220
HFN-130 IND ——
HFN-130 ——
HFN-130 ——

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Population Council

2. DATE OF SUBMISSION
August 6, 1999

3. ADDRESS *(Number, Street, City, State and Zip Code)*
One Dag Hammarskjold Plaza
New York, NY 10017

4. TELEPHONE NUMBER *(Include Area Code)*
(212) 339-0663

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Mifepristone Oral Tablets

6. IND NUMBER *(If previously assigned)*
22,047

7. INDICATION(S) *(Covered by this submission)*
Induction of abortion

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☒ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.
NDA 20-687

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
2 0 2

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☒ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)

FOR FDA USE ONLY

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

MIF 008742

12. CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED. Please refer to submissions 100 & 163.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Irving M. Spitz, M.D.
Senior Scientist
Population Council

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Irving M. Spitz, M.D.
Senior Scientist
Population Council

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE
Sandra P. Arnold	Sandra Arnold

18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
Population Council One Dag Hammarskjold Plaza New York, NY 10017	(212) 339-0663	08/06/99

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

§ 312.7 Promotion and charging for investigational drugs.

(a) *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) *Commercial distribution of an investigational new drug.* A sponsor or investigator shall not commercially distribute or test market an investigational new drug.

(c) *Prolonging an investigation.* A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

(d) *Charging for and commercialization of investigational drugs*—(1) *Clinical trials under an IND.* Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.

(2) *Treatment protocol or treatment IND.* A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided: (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence. FDA must be notified in writing in advance of commencing any such charges, in an information amendment submitted under § 312.31. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

(3) *Noncommercialization of investigational drug.* Under this section, the sponsor may not commercialize an investigational drug by charging a price larger than that necessary to recover costs of manufacture, research, development, and handling of the investigational drug.

(4) *Withdrawal of authorization.* Authorization to charge for an investigational drug under this section may be withdrawn by FDA if the agency finds that the conditions underlying the authorization are no longer satisfied.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 19476, May 22, 1987]

§ 312.10 Waivers.

(a) A sponsor may request FDA to waive applicable requirement under this part. A waiver request may be submitted either in an IND or in an information amendment to an IND. In an emergency, a request may be made by telephone or other rapid communication means. A waiver request is required to contain at least one of the following:

(1) An explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved;

Electronic Mail Message

Date: 6/2/99 3:57:14 PM
From: [redacted]
To: [redacted]
Subject: Re: RU 486

Thanks [redacted]

I'll respond to [redacted] tomorrow. I routed your comments to our CMC team and should have a fax ready to send by then.

again, many thanks!

p.s. if there are any new developments on the pop council NDA, please be sure to let me know. [redacted]

[redacted]

>
>Approvalable letter: September 18, 1996
>It was not only chemistry issues. Clinical, Chemistry, Biopharm.and
>Labeling were the problems. The indication is for induction of
>abortion.
>
>I have been receiving calls form [redacted] orm Exelgyn, would you like for
>me to call her and let her know that you will be handling this action?
>Please let me know if I should call heror you would like to handle this.
>
>Thanks,
>

APPEARS THIS WAY
ON ORIGINAL

1. Brief History of Project

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

2. Status of US Clinical Trials

Total Number of Subjects Enrolled = 2,115

Enrollment Completed on September 1, 1995

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

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

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

3. Status of New Manufacturer

a. **Manufacturer**

i. Contract has been concluded.

ii. New synthesis development is well advanced.

APPEARS THIS WAY
ON ORIGINAL

4. Organization and Content of NDA

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

Item 1. **Index**

Item 2. **Summary**

Item 5. **Nonclinical Pharmacology/Toxicology**

All included studies were previously submitted to IND

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

Item 6. **Human Pharmacokinetics/Bioavailability**

All included studies were previously submitted to IND

4. Organization and Content of NDA (Cont.)

APPEARS THIS WAY
ON ORIGINAL

b. Following NDA Sections Have Unique Features

Item 3. Chemistry, Manufacturing and Controls

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

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

Field Copy (NY District)

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

Item 4. Samples, Methods Validation and Labeling

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

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

4. Organization and Content of NDA (Cont.)

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

Item 8. Clinical

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

All studies are regarded as historically controlled.

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

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

Integrated Summary of Safety will discuss experience in all studies.

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

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

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

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

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.

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.)

APPEARS THIS WAY
ON ORIGINAL

b. Information on New Manufacturer

i. Submission of Drug Master Files

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

E L E C T R O N I C M A I L M E S S A G E

Date: 29-Nov-1995 09:42am EST
From:

Dept: HFD-510 PKLN
Tel No: FAX 301-443-9282

TO:

Subject: RU 486

Re Congressional Request dtd. 10,20 Nov 95 for communications regarding RU 486 from 1 Jan 1992 up to the present for persons listed in the letter to the Commissioner of FDA from Tom A. Coburn, MD, Member of Congress (20 District, Oklahoma): To the best of my recollection I have none other than that which might be a part of documented FDA files.

ROUTING SLIP
GENERATED BY: HF-40
DATE: AUG 02, 2000

FDA CONTROL NUMBER: 00 4974 **TRACER #:** **OS #:**

DATE OF CORRESPONDENCE: 07/24/00 **DATE INTO FDA:** 08/02/00

TO: JANE E HENNEY HF-1

FROM: THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS
AMERICAN MEDICAL ASSOCIATION

SYNOPSIS: MEETING REQUEST FOR DR. HENNEY TO DISCUSS FDA'S RESTRICTIONS ON THE DISTRIBUTION OF MIFEPRISTONE

LEAD OFFICE: HF-1 **HOME OFFICE:** HF-40

CONTACT/PHONE#:

COPIES: GENERAL DISTRIBUTION

COORDINATION:

SIGNATURE REQUIRED:

REFERRALS FROM HF-40

ASSIGNED TO	ACTION	DUE DATE
HF-1	NECESSARY ACTION	08/15/00
REMARKS: PLEASE ADVISE WRUSS OF DECISION. SEE ALSO TRAC #4973 (COPY ATTACHED)		
HF-40	NECESSARY ACTION	08/15/00
REMARKS: WRUSS WILL ADVISE		

ROUTING HISTORY
DATE: AUG 02, 2000

FDA Control Number: 00 4973 Tracer #: OS #:

Date of Correspondence: 07/24/00 Date Into FDA: 08/02/00

To: JANE E HENNEY HF-1

From: THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

Synopsis: ENCLOSES THE AMERICAN COLLEGE OF OBSTETRICIANS & GYNECOLOGISTS' ANALYSIS OF POSSIBLE FDA RESTRICTIONS ON MIFEPRISTONE

Lead Office: Home Office: HF-40

Contact/Phone#:

Date Due Out of FDA: 08/16/00 Closed Date: OPEN

Copies: GENERAL DISTRIBUTION

Coordination:

Signature Required:

Assigned By	Assigned To	Referred Act	Status
HF-40		08/02/00	Referred 08/02/00

Remarks: PLEASE SEND COPY OF RESPONSE TO , HF-40. SEE ALSO TRAC #00-4974

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE GENERAL COUNSEL
FOOD AND DRUG DIVISION
5600 FISHERS LANE, GCF-1
ROCKVILLE, MD 20857

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Job number	:	345
Date	:	Sep-28 11:43
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Start time	:	Sep-28 11:43
End time	:	Sep-28 11:45
Pages sent	:	005
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE GENERAL COUNSEL
FOOD AND DRUG DIVISION
5600 FISHERS LANE, GCF-1
ROCKVILLE, MD 20857

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[redacted]

Nov. 21, 1995

Please search your paper & electronic files and notes for the requested documents and return to _____ by Nov. 29. If you find nothing, please send a message to that effect.

Thank you,

_____

Chuck _____

CONGRESSIONAL REQUEST

CENTER FOR DRUG EVALUATION & RESEARCH
EXECUTIVE SECRETARIAT STAFF
CONTROL FORM

FROM: REPRESENTATIVE TOM A. COBURN, M.D.*

TO : Dr. David A. Kessler

SUBJ: DOCUMENT REQUEST: RU-486

***PLEASE TREAT AS A CHAIRMAN DOCUMENT REQUEST AND PROVIDE ALL DOCUMENTS. REPRESENTATIVE COBURN WILL MOST LIKELY REQUEST THE CHAIRMAN OF THE HEALTH AND ENVIRONMENT SUBCOMMITTEE TO SUBMIT A LETTER IN ORDER TO OBTAIN ALL DOCUMENTS.**

DATE OF DOCUMENT: 11/10/95**

DATE REFERRED : 11/20/95

DUE DATE : **11/30/95**

CONTROL NUMBER : HFD-8-11-14C

OFFICE OF DRUG EVALUATION II REC'D NOV 20 1995

**Not received in CDER until 11/20/95!

ROUTING SECTION

OFFICE	DATE REFERRED			
HFD-1	11/20/95	cc:	HFD-6/ [redacted]	
HFD-2	11/20/95		HFD-6/ [redacted]	
HFD-3	11/20/95			
HFD-4	11/20/95			
HFD-5	11/20/95			
HFD-101/HFD-120	11/20/95	to HFD-510	11/20/95	due 11/30/95 #925
HFD-101/HFD-150	11/20/95	[redacted]	11/20/95	due 11/30/95 #926
HFD-300	11/20/95			
HFD-102/HFD-510	11/20/95	Rec'd 11/21/95		
HFD-210	11/20/95			

INSTRUCTIONS: DOCUMENT REQUEST.

REMARKS: Documents thru HFD-1/ [redacted] WOC 2, Room [redacted]

HAND CARRY, PLEASE.

COMMENTS:

+L

MIF 008791

TOM A. COBURN, M.D.
2D DISTRICT, OKLAHOMA
COMMITTEE ON COMMERCE
SUBCOMMITTEES
TELECOMMUNICATIONS AND FINANCE
HEALTH AND ENVIRONMENT
ENERGY AND POWER

511 CANNON HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225-2701
(202) 225-3038 (FAX)

215 STATE STREET, SUITE 815
MUSKOGEE, OK 74401
(918) 687-2533
(918) 682-3503 (FAX)

Congress of the United States
House of Representatives
Washington, DC 20515-3602

November 10, 1995

Dr. David A. Kessler
Commissioner
U.S. Food and Drug Administration
Room 14-71
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Kessler:

As a member of the House Commerce Committee's Subcommittee on Health and the Environment, I write to request copies of documents in the possession of the Food and Drug Administration, including any of its advisory committees, relating to the drug known as RU 486 (mifepristone), developed by the company Roussel Uclaf SA.

I understand that the Population Council has an active investigational new drug application (IND) to use RU 486 for abortion. Several reports have appeared which indicate extensive communications between representatives of the Clinton administration and private companies and organizations, including the Population Council, concerning the future availability of RU 486 for use as an abortion pill in the United States. These reports, together with issues raised in a Citizens' Petition on RU 486 recently submitted to the FDA, have generated serious concern for public safety and the integrity of the drug approval process. Consequently, I am requesting that you provide the following information:

1) Any and all written or recorded communications, including electronic or telephonic communications, to or from the persons listed below relating to RU 486 from January 1, 1992 up to the present (i.e., up until the time the document search is conducted).

When used in the above request, the word "communication" includes, but is not limited to: correspondence, electronic mail, memoranda, notes of conversations, notes of meetings, copies of the calendars of meetings, and telephone logs and message slips. It also includes all communications which do not specifically mention RU 486 but which may relate to its possible approval by FDA for use as an abortifacient (eg., communications relating to the acceptability of foreign data in the drug approval process).

For each such communication, please indicate the date of the communication, the names and the professional or organizational affiliations of all persons involved or present, the locations of meetings, and the offices within the FDA from which the communications were obtained. Also, please indicate which communications, if any, are confidential and may not be disclosed to the public.

This request includes all communications sent to or by the following persons from January 1, 1992 up to the present:

President Clinton, Mrs. Clinton, and White House staff
Other administration officials or personnel, including yourself, your assistant ——— ———, and ——————— of the Endocrine Drugs Division of the FDA
Edouard Sakiz, Dr. Andre Ulmann, and other officers, employees, or representatives of Roussel Uclaf
Margaret Catley-Carlson, Dr. Wayne Bardin, and other officers, employees, and representatives of the Population Council
David A. Grimes, M.D.
Daniel R. Mishell, M.D.
Suzanne Poppema, M.D.
Officers, employees and representatives of the following companies and organizations:
Hoechst AG of Frankfurt, Germany
Hoechst Celanese Corporation of Somerville, New Jersey
Hoechst-Roussel Pharmaceuticals of Somerville, New Jersey
Rhone-Poulenc of Paris
Schering AG of Berlin, Germany
G.D. Searle Company of Skokie, Illinois
Upjohn Company of Kalamazoo, Michigan
Gynopharma, Inc. of Somerville, New Jersey
Cabot Medical Corporation of Langhorne, Pennsylvania
Aurora Medical Services of Seattle, Washington
Fund for the Feminist Majority
Planned Parenthood Federation of America
Reproductive Health Technologies Project
National Abortion Federation
National Abortion and Reproductive Rights Action League (formerly the National Abortion Rights Action League)
Oregon Science Health University of Portland, Oregon
Center for Reproductive Law and Policy
National Organization for Women
Women's Issues Network

2) Any and all documents relating to the implementation of President Clinton's January 22, 1993, memorandum for the Secretary of Health and Human Services regarding the importation of RU 486.

In this memorandum, the President asked the Secretary to take the following three actions:

a) "promptly instruct the FDA to determine whether there is sufficient evidence to warrant exclusion of RU-486 from the list of drugs that qualify for the personal use importation exemption;"

b) "immediately take steps to rescind Import Alert 66-47" if the "FDA concludes that RU-486 meets the criteria for the personal use importation exemption;" and

c) "promptly assess initiatives by which the Department of Health and Human Services can promote the testing, licensing, and manufacturing in the United States of RU-486 and other antiprogestins."

When used in the above request, the word "document" includes, but is not limited to: internal and external documents of the Food and Drug Administration, documents prepared by persons or offices outside the FDA (including documents prepared by non-governmental persons, organizations, or companies), correspondence, electronic mail, memoranda, notes of conversations, notes of meetings, copies of the calendars of meetings, and telephone logs and message slips. It also includes all documents which do not specifically mention RU 486 but which may relate to its possible approval by FDA for use as an abortifacient (eg., criteria for the acceptance of foreign data, etc.). For each such document, please indicate the date of the document, the author or authors of the document, the persons to whom it was given or sent, and the offices within the Department from which the documents were obtained. Please separate the documents in this second request into three categories based on which of the three actions requested by the President the documents address. Again, please indicate which communications, if any, are confidential and may not be disclosed to the public.

Thank you for your attention to this inquiry. A similar request for documents has been submitted to Secretary Shalala. I look forward to receiving the information by December 1, 1995. If you foresee any difficulty in fulfilling this request by that date, please notify me immediately. Roland Foster on my staff will be available to work with you if you have any questions.

Sincerely,

Tom A. Coburn, M.D.
Member of Congress

NOTE

IND [redacted]

The Population Council

Submission: 17 May 1985

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Amendment dated 17 May 1985

RU 38486

Antiprogestin - Antiglucocorticoid

Intended Use: [redacted] as an early abortifacient.

Related: IND [redacted]

Preclinical Studies:
26-Week Oral (Gavage) Toxicity Study of RU 38486 In Charles River Rats. RSL 613/84260, [redacted]
Report dtd 27 Dec 1984. Start of treatment 19 April 1983.

QA - Signed: [redacted]
Quality Assurance

Dose: 0, 5, 25, 125 mg/kg/day by oral gavage as a suspension in 1% methylcellulose in water 7 days/week for 26 weeks. Groups 1-4 respect.

No. Animals: 20M;20F Charles River CD rats per group. ca. 28 days old

Results:
Mortality: 2 Females, 1 control and 1 high dose (also had marked kidney lesions) - apparently due to anesthetic/blood withdrawal trauma.
Clinical Signs: Increased salivation at 125 mg/kg; some at 25 and occasionally at 5 mg/kg. Pink swellings in urogenital region - females, dose related (0, 10, 40, 68%). Fur loss (mainly dorsum and scapular)- 5 and 25 mg/kg greater than controls, 125 mg/kg only in a few. Hypersensitivity to external stimuli - 50% of 25 mg/kg F, 1 control and low incidence M&F of other groups. 1st 8 wks rapid vibration of pinnae immed. before or after dosing in 9/20F on 25 mg/kg and 2/20F on 125 mg/kg. Sialodacryo-adenitis and signs of infection - all groups wks 1-5.
Bodyweights: Males - 25 and 125 mg/kg gained less than controls. Females - 5 and 25 mg/kg slightly greater and 125 mg/kg slightly less than controls.

Table of Contents

cc: Original IND [redacted] HFD-345;
HFD-510 IND [redacted] HFD-510 [redacted] HFD-510 [redacted] Pharmacologist

Food Consumption: Dose related increase for all treated female groups. Utilization efficiency - lower for 25 and 125 mg/kg M and 125 mg/kg F.

Water Consumption: Females - dose related increase.

Ophthalmoscopy: No apparent effect.

Vaginal Smears: (Daily wks. 1-2 and wks. 7-9) Mean no. days cornified cells observed was greater for treated than controls.

Cardiac Effects: Females - heart rates marginally lower at 25 and 125 mg/kg. Blood pressure considered unaffected.

Hematology: **RBCs, Hb, PCV** - lower in treated females (5 mg/kg from wk. 12); **Hb** slightly lower for 125 mg/kg M (transient at 5 mg/kg). **Platelets** - higher for: 125 mg/kg F, 25 mg/kg F wks 5 and 12, 5 mg/kg F wk. 5 only. **Thrombotest times** - shorter for 125 mg/kg M&F (wk 24 and F wk 12, 5 and 25 mg/kg, F wk 12 also shorter than C which were slightly longer than expected). **Neutrophils** - slightly higher for 125 mg/kg F, and less marked for 25 mg/kg F wks 5 and 24 and 5 mg/kg F wk 24.

Clinical Chemistry: **Glucose** - lower for treated F (sl for 5 & 25 mg/kg). **Total Protein** - higher for 125 mg/kg M&F (due to sl higher albumin and beta globulin), sl higher for 25 mg/kg M and 5 mg/kg M&F. **SGOT** slightly lower than C for 125 mg/kg M&F. **Cholesterol** - 125 mg/kg M&F higher than controls. **Triglycerides** - sl lower 125 mg/kg M&F; 5 mg/kg M (and some F) sl higher than C wks 12 and 24. **Phospholipids** - Higher for 125 mg/kg F, also for few in ea. M treated and 5 and 25 mg/kg F gps. **Electrolyte disturbances** - Na^{+} for 125 mg/kg M at wks 12 and 24 was higher and F lower than controls. Cl^{-} for 125 mg/kg F were sl lower than controls (also some at 25 mg/kg). Also lower - 25 mg/kg M wk 5, 5 mg/kg M&F wks 12 and 25, and 125 mg/kg M wk 25. Ca^{++} for 125 mg/kg F sl higher all periods (similar non-dose rel in 5 and 25 mg/kg F wk 24).

Urinalysis: 125 mg/kg M (also 5 mg/kg M wk 12) and all treated F gps urine more acidic than controls. Some 25 and 125 mg/kg M&F voided urine with more protein than controls usually associated with sl higher SpG. Occasional 5 mg/kg rats showed similar findings.

24 hr. Urinalysis - 25 and 125 mg/kg F voided more urine than controls, assoc. with greater water intake wks 13 and 25. 25 mg/kg F had more sodium, potassium, chloride and creatinine in the urine than contols. 25 mg/kg M wks 5 and 13 (and less apparent wk 25) voided more urine than controls with creatinine levels sl higher wk 13.

Feces - No occult blood.

Hormone Assays: **Cortisone** - higher for some 125 mg/kg M&F (F wide variation - non sig.). **ACTH** - lower than controls for 25 and 125 mg/kg F with no obvious corticosterone effects. **Estradiol** - sl lower for 25 and 125 mg/kg M; higher for 25 mg/kg F wk 5. **Progesterone** - 25 and 125 mg/kg F wk 5 markedly higher than controls, also some 5 mg/kg F. Became less apparent and by wk 24 similar to or lower than controls. **Testosterone** - occasional high value in 125 mg/kg M, but in general similar to controls.

Organ Weights: **Pituitary** - treated F non dose-related increase; males similar to controls. **Adrenals** - F dose rel (5 mg/kg sl) increase; males sim to controls. **Thyroid** - 125 mg/kg F and treated males sl higher than controls. **Thymus** - treated M&F less (non sig) than C. **Liver** - 25 and 125 mg/kg M&F increased over controls; 5 mg/kg F similar but less marked increase. **Kidney** - 25 mg/kg F and 125 mg/kg M&F greater than C. **Prostate, Seminal Vesicle and Testes** - lower for 125 mg/kg M. Lower SV and Prostate wts for 25 mg/kg M. Sl lower SV wt-s for 5 mg/kg M. **Uterus** - Lower for all treated F gps. **Ovary** - 5 mg/kg gp F only lower than C. **Heart** - Absol. sim to C; 125 mg/kg F rel sl higher than C.

Gross Pathology: Alopecia - 5 and 25 mg/kg F higher than C. **Pituitary** - most in all treated F gps and 2 C enlarged. **Adrenals** - a number of 25 and 125 mg/kg F and one 5 mg/kg F enlarged; Males similar to C.

Thyroids - enlarged in 3M;2F 125 mg/kg and 1F on 5 mg/kg. **Kidney** - hydronephrosis sl increased in treated F. **Prostate, Seminal Vesicle and Testes** - 125 mg/kg M flacid/small testis greater incidence than C, also dose related
increased incidence of empty SV and small prostates. **Mammary glands** - thickened and/or with creamy cysts in majority of treated F.

Histopathology:

Thymus - slight increased incidence of early involution in high dose males (5/20 vs 2/20 controls).

Liver - dose-related increase of minimal centrilobular hepatocyte enlargement in high dose M and F (also 25 mg/kg F). Not seen in C or low dose.

Spleen - incidence of hemosiderosis increased in 125 mg/kg females. Slight dose related increase at other levels.

Kidneys - both sexes showed a dose-related increased incidence of basophilic dilated tubules. Severity was also dose related in F. For some animals (mainly F) this was associated with glomerular hyalinization/sclerosis and minimal interstitial fibrosis.

Thyroid - follicular epithelium height was increased in high dose females. There was also a dose-related incidence in all treated male groups. One high dose F had a follicular adenoma; one high dose M had a focus of cystic follicles.

Adrenals - incidence of increased cortical width in all groups of treated F was dose-related.

Pituitary - majority of treated F in all groups had diffuse hyperplasia of the pars anterior.

Testes - spermatogenesis reduced in 4 high dose males.

Seminal Vesicles - incidences of reduced colloid was dose-related in treated males (all groups) and mid and high dose M had reduced height of epithelium.

Prostate - treated males (all groups) dose-related incidence of reduced colloid.

Ovaries - corpora lutea absent in majority of F in all treated groups with ovarian cysts (dose-related) in a small proportion of them.

Uterus - reduced endometrial stroma in all treated F with a dose-related incidence of dilation of endometrial glands.

Cervix/Vagina - compared to controls rats from all treated groups showed an increased incidence (not dose-related) of keratinized/non-keratinized stratified squamous epithelium.

Mammary glands - dose-related distention of acini and ducts; severity was also dose-related.

6-Month Oral (gastric intubation) Toxicity Study of RU 38486 In Cynomolgus Monkeys. RSL 604/84146 [redacted] Report dtd 10 January 1985. Start of treatment 16 June 1983.

QA - Signed: [redacted], Quality Assurance

Dose: 0, 5, 15, 45 mg/kg/day orally by gastric intubation as a suspension in 1% methylcellulose in water 7 days/week for 26 weeks.

No. Animals: 5M;5F young adult Cynomolgus monkeys (Macaca fascicularis) per group.

Results:

Mortality: None

Clinical Signs: Sometimes salivation and vomiting - mainly at 45 mg/kg. (The time of vomiting in relation to dosing varied considerably, including some animals which vomited overnight - 171M and 166F frequent vomiting.) Menstrual activity of all dosed females ceased promptly following the start of dosing. (During the dosing period the maturation indices for the treated groups were generally slightly higher than controls.)

Body Weights: During the first few weeks of dosage a significant loss of weight at 45 mg/kg with a lesser loss at 15 mg/kg followed by a normal weight gain. All five 45 mg/kg males also lost weight during the final 2-3 wks. of dosing.

Food and Water Consumption: A significant reduction in food consumption weeks 1-5 for the 45 mg/kg group and a smaller effect for the 15 mg/kg group. Although not significant, some water reduction was noted coincident with the reduced food consumption.

Ophthalmoscopic Exam: No treatment-related changes.

Electrocardiogram: Heart rates were reduced for males in the 45 mg/kg group during weeks 7 and 25.

Hematology: Mean platelet counts for the 45 mg/kg group were significantly lower than controls weeks 6 and 24.

Blood Chemistry: At 45 mg/kg serum ACTH was increased, cholesterol was reduced and there was a transient rise in triglycerides. Serum cortisol was increased at 15 and 45 mg/kg. Females at 15 and 45 mg/kg generally had lower estradiol and higher LH levels. Females at all three dose levels had reduced serum progesterone concentrations.

Urinalysis: Excretion of potassium and chloride was reduced at all three dose levels. Sodium excretion was reduced at 45 mg/kg.

Fecal Occult Blood Tests: No evidence of a treatment-related effect.

Preterminal Bone Marrow Examination: Normal

Organ Weights: Kidney and adrenal weights were significantly increased for all three dosed groups. Liver weights were sig. higher for 15 and 45 mg/kg groups. Pancreas wts. were sig. lower for the 45 mg/kg group.

Gross Pathology:

Adrenals - Dark coloration in 1 on 5 mg/kg, 1 on 15 mg/kg, and 7 on 45 mg/kg.

Kidneys - Small subscapular foci in 3 on 5 mg/kg, 2 on 15 mg/kg, and 2 on 45 mg/kg.

Ovaries - Cystic ovaries or parovarian cysts in 3 on 5 mg/kg, 3 on 15 mg/kg, and 2 on 45 mg/kg.

Fallopian tubes - Cystic dilatation/enlarged in 5 on 5 mg/kg, 4 on 15 mg/kg, and 3 on 45 mg/kg.

Histopathology:

Liver - Increased amounts and incidence of lipofuscin (brown pigment) in treated monkeys (not dose-related).

Kidneys - Areas of cortical scarring, cortical cysts and an increased incidence of subscapular foci of fibrosis was seen in treated animals.

Adrenals - Increased eosinophilia of the zona fasciculata, with loss of distinction between the zona fasciculata and zona reticularis in 5/5 M and 1/5 F on 45 mg/kg, and 1/5 M on 15 mg/kg. Remaining 4/5 F on 45 mg/kg had increased width of the zona reticularis.

Thyroids - Increased incidence of brown pigment within follicular epithelium of 45 mg/kg group.

Ovaries - Most treated F monkeys had dilated follicles and an absence of corpora lutea. Multiple large follicles were present in 2 on 15 mg/kg and 1 on 45 mg/kg. All controls cycled normally.

Uterus - Most treated had a thin endometrium usually with few endometrial glands and a dilated lumen and/or dilated endometrial glands. Some monkeys had focal mucosal hyperplasia, squamous metaplasia and inflammatory cell infiltration (not dose-related). 3/5 on 15 mg/kg and 3/5 on 45 mg/kg had compact endometrial stroma. Normal cyclic activity was seen in controls.

Cervix - Squamous metaplasia, inflammatory changes and mucosal hyperplasia were seen in most treated. Incidence and severity were not dose related. The incidence of mucosal hyperplasia was increased at 15 and 45 mg/kg.

Vagina - Moderately keratinized in treated monkeys. One control (all normal cyclic act.) had only focal keratinization.

Fallopian Tubes - Lumen dilated, often markedly, in most treated F monkeys. A few monkeys also had mucosal hyperplasia and salpingitis. Incidence and degree of changes were not dose-related.

Mammary Glands - A little increase in the degree of development (not dose related) without increased secretion.

Testes - Some in all treated groups showed a reduction of spermatogenesis - as atrophic tubules with increased interstitial connective tissue or loss of spermatic epithelium or arrest of spermatogenesis.

Other histopathological changes were similar to control or considered by the sponsor to be unrelated to drug treatment.

Comments and Conclusion:

The antiprogestin-antiglucocorticoid, RU 38486, has been proposed for the [redacted] as an early abortifacient under subject IND. Clinically doses of [redacted]

26 Week studies were carried out in rats at doses of 0, 5, 25, and 125 mg/kg and in monkeys at doses of 5, 15 and 45 mg/kg.

With regard to the rat study, hematological changes appeared to be attributable to the antiprogesterone component of the drug while the various minor clinical chemistry alterations appear to be the result of antiglucocorticoid activity. There were no observable renal differences between the 5 mg/kg males and the controls. The sponsor indicates, however, that the renal lesions seen in females at all doses and the males at 25 or 125 mg/kg bore resemblance to those of spontaneous progressive glomerulonephrosis, which may reflect a premature aging due to overdosage with the test drug. This may or may not be true although it appears that in the rat these findings were compound related. The occurrence of prominent hemosiderosis in over half of the females at 125 mg/kg, also showing a marginal anemia, would appear to be related to drug administration.

Treatment-related changes in females included an increased occurrence of cornified cells in vaginal smears, decreased uterine and ovarian weights, increased adrenal cortical widths, diffuse hyperplasia in the pars anterior, an absence of corpora lutea, reduced uterine endometrial stroma, absence of uterine pseudo-stratified columnar epithelium and increased incidence of distended mammary acini and ducts.

Findings in male rats included reduced prostatic and seminal vesicle colloid, and reduced spermatogenesis.

A variety of changes were induced in monkeys receiving RU 38486 which were not seen in control animals. It would appear that the overall effects are related to various minor disturbances of metabolic processes which were modulated by glucocorticoid hormones and/or modification of tissues due to unphysiological estrogen/progesterone balance. All treated groups showed an increase in the incidence of brown pigment in the hepatocytes which may or may not be due to an increased metabolic activity caused by RU 38486. Although the incidence and severity of the changes did not increase with increasing dosage, the significance of the histopathological findings of areas of cortical scarring, cortical cysts and increased incidence of subcapsular foci of fibrosis of the kidneys is unclear. Some of the changes were also observed in the controls.

Findings with the low dose of RU 38486 (5 mg/kg) were more or less confined to cessation of menstrual activity with consequent physiological changes in the histological appearance of the reproductive organs for females and decreased spermatogenesis in one male. Pharmacological effects were usually increased at higher doses.

In general in the rat and monkey studies there were no unexpected findings and observed effects are basically considered predictable consequences of pharmacological suppression of glucocorticoid and progesterone activity.

Our letter to the sponsor dtd 15 April 1985 requested that both hematological parameters and liver function be closely and carefully monitored in all patients receiving RU 38486.

From the standpoint of Pharmacology, no action is deemed necessary at this time.

[redacted]

cc:
Original IND [redacted]
HFD-345
HFD-510 IND [redacted]
HFD-510 [redacted]
HFD-510 [redacted]

APPEARS THIS WAY
ON ORIGINAL