In a recent publication reporting the results of research work, JOST (1986) used the antiprogesterone property of RU·38486 to verify "the role of a progesterone deficiency in abnormalities of pregnancy and foetal development" in the female rabbit.

Pregnant females of the Burgundy Fawn race were treated subcutaneously with 2 daily injections for 1, 2, 3 or 5 days from day 11 of pregnancy. The administered doses were 0.250, 0.500, 0.750 and 1 mg/animal/day, or in other words, for an estimated weight of about 3 kg per rabbit, doses ranging from 0.08 to 0.33 mg/kg/day. The author observed a number of total or partial interruptions of pregnancy related to the total dose administered. In the surviving foetuses several malformations of the cranium were observed (failure of the cranial vault to close and haemorrhagic destruction of the upper part of the head and brain, no spinal column, no closure of the eyelids).

These malformations were of the same type as those observed in our own studies and supports the involvement of RU 38486 in their genesis.

2. Study of the oestrous cycle in the rat

Justification for not performing the fertility study.

Before undertaking the fertility study required by legislation, it seemed necessary to confirm the expected effect of treatment on the oestrous cycle.

RU 38486 was administered to mature virgin Sprague-Dawley rats for 3 weeks at doses of 0, 0.25 and 1 mg/kg. The vaginal smears were examined daily during this period and then for the following 5 weeks.

Treatment at each of the doses considerably disrupted the oestrous cycle, causing blockade at around the stage of oestrus within about ten days. Withdrawal of treatment produced a gradual restoration of the cycle over 2 or 3 weeks. Total functional recovery was confirmed by mating the females with untreated males. The reproductive capacity then proved perfectly normal.

This study showed the rapid, total and relatively prolonged action of RU 38486 in the rat at doses as low as 0.25 mg/kg. As the induction of blockade of the cycle was well established, it then became impossible to hope for fertilisation of these animals and hence a pregnancy which would allow the offspring to be examined.

The regulatory fertility study was therefore not performed.

3. Peri- and postnatal study in the rat

The impossibility of performing a fertility study due to the properties of RU 38486 resulted in the definition of an extended protocol for a large scale peri- and postnatal study in two successive generations.

Pregnant rats were treated with doses of 0, 0.25, 0.50 and 1 mg/kg from day 15 of pregnancy to day 21 postpartum. Each group was composed of about 20 females.

Interruptions of pregnancy were observed at doses of 0.50 mg/kg (2 cases out of 19) and 1 mg/kg (8 cases out of 21). The females which were allowed to go to full term littered at the normal time and displayed normal behaviour towards their offspring during lactation.

The various parameters relating to the offspring (appearance, survival, growth up to maturity, etc.) were not modified by treatment. Similarly, a battery of tests to assess their locomotor development, induced behaviour or spontaneous activity revealed no disturbances attributable to RU 38486.

Lastly, reproductive function evaluated by production of the F_2 generation appeared perfectly normal in all the treated groups.

4. Studies of the combination of RU 38486 and progesterone

It appeared of interest to try to antagonise the abortifacient action of RU 38486 (orally) with progesterone (subcutaneously) and then to observe the outcome of pregnancy and the morphology of the full term foetuses.

4.1. Study in the rat

Pregnant females received RU 38486 and, a few hours later, progesterone from day 6 to day 12 of pregnancy at doses of 2 + 50 mg/kg or 2 + 100 mg/kg, respectively.

These two dosage pairs enabled the pregnancy to be maintained under normal conditions.

Progesterone alone, administered at doses of 50 and 100 mg/kg, displayed no particular activity.

It should be remembered that RU 38486 alone in a dose of 2 mg/kg proved very abortifacient in an embryotoxicity study (81% foetal losses).

4.2. Study in the rabbit

Pregnant rabbits received RU 38486 and progesterone from day 6 or 7 until day 15 of pregnancy in doses of 4 + 100 mg/kg and 8 + 100 mg/kg. As in the rat, the pregnancy developed normally with the two pairs of doses in comparable fashion to that in the controls.

Progesterone alone in a dose of 100 mg/kg proved without effect on pregnant females, whereas RU 38486 alone, at doses of 4 or 8 mg/kg, caused abortion in the majority of animals (65 to 100% foetal losses).

The cause of the celosomia in a surviving foetus from a dam receiving the 8 mg/kg dose remained undetermined. In this study it appeared that the sixth day of gestation was a time of particular susceptibility to the action of RU 38486 on the pregnancy.

Thus, these studies show that the abortifacient activity of RU 38486 can be antagonised by progesterone and allow the pregnancy to develop normally.

GENETIC TOXICOLOGY

The single dose treatment proposed for human therapy with RU 38486 considerably reduces the potential risk of a mutagenic effect. Nevertheless this potential, however minimal, was tested at three levels of genotoxic damage: gene mutations, chromosomal aberrations and repair of lesions in DNA.

1. Detection of gene mutations: Ames tests

Five strains of Salmonella typhimurium recommended by ——— were used (TA 1535, TA 100, TA 1537, TA 1538 and TA 98) in the absence and presence of an S-9 mix metabolic activation system composed of hepatic microsomes obtained from Aroclor 1254-induced rat liver with the addition of cofactors.

RU 38486 in solution in dimethylsulphoxide was tested at concentrations ranging from 100 to 10000 µg/dish. The vehicle alone acted as a negative control and four substances acted as positive controls, depending on the strain and the action if any of the activation system.

During two successive trials no increase in the number of spontaneous mutants appeared both in the absence and in the presence of metabolic activation. RU 38486 therefore did not prove to be mutagenic in this test.

2. Detection of chromosomal aberrations: micronucleus test in the mouse

The mutagenic potential or, more precisely, the clastogenic effect of RU 38486 was tested in male and female Swiss mice by observing the frequency of micronucleii in the young erythrocytes of the bone marrow.

RU 38486 suspended in an aqueous solution of 0.25% carboxymethylcellulose was administered in a single dose of 1000 mg/kg, considered to be the maximum tolerable dose.

The vehicle alone acted as a negative control, while triethylenemelamine in a dose of 0.25 mg/kg and dimethylbenzanthracene in a dose of 25 mg/kg served as positive controls. The animals were killed 24, 48 or 72 hours after treatment.

At no timepoint did the spontaneous frequency of micronucleated polychromatic erythrocytes appear to be increased under the effect of treatment with RU 38486.

Thus no mutagenic action was demonstrated in the mouse.

3. Repair of lesions in DNA: unscheduled DNA synthesis in cultured human HeLa cells

RU 38486 in solution in dimethylsulphoxide was tested at doses of 1, 5, 10, 50 and 100 µg/ml. The last dose precipitated out in the culture medium and therefore could not be exceeded. A metabolic activation system (S-9 mix) was used with the same composition as for the Ames test. Dimethylsulphoxide acted as a negative control. Methylmethanesulphonate and cyclophosphamide served as positive controls with and without metabolic activation.

The repair of any lesions caused by RU 38486 in human HeLa cells was evaluated by adding tritiated thymidine, used for the synthesis of DNA, to the culture medium and assaying it at the end of the test by a technique.

No statistically significant increase in the incorporation of tritiated thymidine was found at any of the doses in the absence and in the presence of metabolic activation.

RU 38486 therefore caused no mutagenic effect in HeLa cells.

CONCLUSION

RU 38486 proved to have little if any toxicity in a single dose of 1000 mg/kg in the mouse, rat or dog. Treatment lasting 1 month or 6 months in the rat and monkey revealed no genuine toxicity. The observed effects found expression in the form of biochemical variations and modifications in bodyweight and histopathological findings in the organs targetted by the antiglucocorticoid, antiprogesterone and anti-androgenic activities of RU 38486. The monkey, in this case, proved more sensitive than the rat to these endocrine disorders.

In view of the proposed treatment conditions whereby RU 38486 is to be administered in a single dose only, long-term studies in animals were not considered of interest.

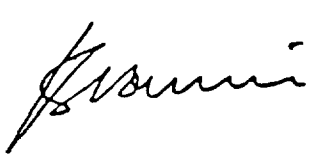
Reproductive studies clearly confirmed the abortifacient action of RU 38486. In this respect the compound proved active in repeated daily doses of 0.5 mg/kg in the mouse, 1 mg/kg in the rat and 2 mg/kg in the rabbit during organogenesis. No teratogenic effect was observed in rodents. In the rabbit however the aetiology of a few isolated malformations, involving the encephalon in particular, remained suspect, implying a possible action by RU 38486. The results of work by A. JOST performed in another strain of Rabbits under somewhat less severe treatment conditions than ours (lower doses, shorter period) describe malformations which resemble those occurring during our studies. The author believes the presence of these abnormalities can be attributed to an effect of retraction of the uterus related to the antiprogesterone activity of RU 38486 before or during the formation of the chondrocranium, rather than to a direct action of the compound on the embryo. In this respect, as we have shown, supplementary treatment with progesterone in a dose of 100 mg/kg totally suppressed the abortifacient effect of RU 38486. No malformations were then observed. Whatever the exact mechanism involved in the genesis of the malformations in the rabbit, the responsibility of treatment with RU 38486 appears in the final analysis to be probable.

The rapid and relatively prolonged blockade of the oestrous cycle in the rat precluded a fertility study. However an extensive peri- and postnatal study demonstrated the absence of any impairment of reproductive function in the offspring of dams treated at the end of pregnancy.

Lastly, RU 38486 did not prove mutagenic in the tests used to represent the possible endpoints of genotoxicity.

In conclusion, RU 38486 is a product which has little toxicity and which in these studies clearly demonstrates the antihormonal properties revealed by pharmacological research. To this expected combination of effects, enhanced by the treatment design inherent in toxicology studies, should be added a probable indirect activity by RU 38486 on the foetus in the rabbit but not in the rat and mouse. By way of precaution, in women this will necessitate the implementation of the appropriate steps to ensure the therapeutic purpose is fully achieved.

24 September 1987



B. VANNIER
Pharmacological and Toxicological Expert

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ACUTE ORAL TOXICITY IN THE MOUSE

Ref. AP 53

SPECIES + STRAIN	NUMBER OF ANIMALS + SEX/GROUP	ROUTE OF ADMINISTRATION	DOSE / DOSAGE FORM	OBSERVATION PERIOD / TIME OF DEATH	APPROXIMATE LETHAL DOSE	SYMPTOMS
Swiss CD1 Mouse		oral, by gavage	1000 mg/kg	21 days observation	not calculated	For 10 days:
	10 males		micronised	No mortality	> 1000 mg/kg	Arched back, Slight difficulty in walking, Abdominal distension
	10 males		non-micronised	No mortality	> 1000 mg/kg	
	10 females		micronised	No mortality	> 1000 mg/kg	Arched back, Slight difficulty in walking
	10 females		non-micronised	No mortality	> 1000 mg/kg	
			in suspension in an aqueous solution of 0.25% carboxy-methylcellulose			

ACUTE ORAL TOXICITY IN THE RAT

Ref. AP 51

SPECIES + STRAIN	NUMBER OF ANIMALS + SEX/GROUP	ROUTE OF ADMINISTRATION	DOSE / DOSAGE FORM	OBSERVATION PERIOD / TIME OF DEATH	APPROXIMATE LETHAL DOSE	SYMPTOMS
Sprague-Dawley CD1 Rat		oral, by gavage	1000 mg/kg	14 days observation	not calculated	During the first 3 days
	10 males		micronised	1 death on day 1	> 1000 mg/kg	Pilo-erection Arched back Slight hypotonicity Abdominal distension
	10 males		non-micronised	No mortality	> 1000 mg/kg	
	10 females		micronised	No mortality	> 1000 mg/kg	
	10 females		non-micronised	No mortality	> 1000 mg/kg	
			in suspension in an aqueous solution of 0.25% carboxy-methylcellulose			

ACUTE INTRAPERITONEAL TOXICITY IN THE MOUSE

Ref. AP 54

SPECIES + STRAIN	NUMBER OF ANIMALS + SEX/GROUP	ROUTE OF ADMINISTRATION	DOSE / DOSAGE FORM	OBSERVATION PERIOD / TIME OF DEATH	APPROXIMATE LETHAL DOSE	SYMPTOMS
Swiss CD1 Mouse		intraperitoneal	1000 mg/kg	21 days observation	not calculated	For about 10 days:
	10 males		micronised	1 death on day 2 1 death on day 3	> 1000 mg/kg	Arched back Slight difficulty in walking
	10 males		non-micronised	No mortality	> 1000 mg/kg	Abdominal distension
	10 females		micronised	1 death on day 3 1 death on day 6	> 1000 mg/kg	Arched back Slight difficulty in walking
	10 females		non-micronised	No mortality	> 1000 mg/kg	
			in suspension in an aqueous solution of 0.25% carboxy-methylcellulose			

ACUTE INTRAPERITONEAL TOXICITY IN THE RAT

Ref. AP 52

SPECIES + STRAIN	NUMBER OF ANIMALS + SEX/GROUP	ROUTE OF ADMINISTRATION	DOSE / DOSAGE FORM	OBSERVATION PERIOD / TIME OF DEATH	APPROXIMATE LETHAL DOSE	SYMPTOMS
Sprague-Dawley CD1 Rat		intraperitoneal	1000 mg/kg	14 days observation	not calculated	During the first week:
	10 males		micronised	3 deaths on day 1 1 death on day 2	> 1000 mg/kg	Arched back
	10 males		non-micronised	No mortality	> 1000 mg/kg	Abdominal distension
	10 females		micronised	2 deaths on day 3	> 1000 mg/kg	Slight difficulty in walking
	10 females		non-micronised	No mortality	> 1000 mg/kg	
			in suspension in an aqueous solution of 0.25% carboxy-methylcellulose			

ACUTE ORAL TOXICITY IN THE DOG

Ref. 87453/TX

SPECIES + STRAIN	NUMBER OF ANIMALS + SEX/GROUP	ROUTE OF ADMINISTRATION	DOSE / DOSAGE FORM	OBSERVATION PERIOD / TIME OF DEATH	APPROXIMATE LETHAL DOSE	SYMPTOMS
Beagle Dog	3 males 3 females	oral (capsules)	1000 mg/kg micronised and presented in gelatine capsules	14 days observation No mortality	not calculated > 1000 mg/kg > 1000 mg/kg	On day 2: Diarrhoea Moderate vomiting (3 animals) Slight weight loss

30 DAY ORAL TOXICITY IN THE RAT

Ref. AL 34

SPECIES + STRAIN	NUMBER OF ANIMALS + SEX/GROUP	DURATION	ROUTE OF ADMINISTRATION	DOSAGE FORM	DOSE + FREQUENCY
Sprague-Dawley CD1 Rat	10 males (M) 10 females (F) per dose	30 days	oral, gastric tube	Micronised powder in suspension in an aqueous solution of 0.25% sodium methylcellulose + 0.20% polysorbate 80.	0 mg/kg/day 8 mg/kg/day 40 mg/kg/day 200 mg/kg/day Once daily

RESULTS: see following pages.

The incidents reported are considered to be attributable to treatment (the figures refer to the number of animals concerned).

30-DAY ORAL TOXICITY IN THE RAT

Ref. AL 34

	DOSES MG/KG/DAY 8	40	200
BIOCHEMISTRY			
Moderate decrease in cholesterol (M)	-	X	X
Moderate decrease in glucose (F)	-	X	X
Moderate decrease in albumin (M,F)	-	X	X
Moderate decrease in alkaline phosphatase (M)	-	-	X
Moderate increase in urea (M,F)	-	-	X
URINALYSES			
Increased excretion of Na, Cl (F)	-	-	X
Decrease in alkaline phosphatase (F)	-	X	X
HAEMATOLOGY			
Moderate increase in activated partial thromboplastin time and platelet count (M,F)	-	X	X
	-	-	X
Increase in red blood cell count (F)	-	-	X

	DOSES MG/KG/DAY 8	40	200
BEHAVIOUR			
Mod. retardation of weight gain after week 3 (M)	-	-	X
Temporarily increased water consumption (M, F)	X	X	X
Moderate decrease in blood pressure (M)	-	-	X
MACROSCOPIC EXAMINATION			
Atrophy of seminal vesicles and prostate	-	X	X
ORGAN WEIGHTS			
Increase in liver (M,F)	-	X	X
Increase in kidneys (F)	-	X	X
Increase in thyroids (M,F)	-	X	X
Decrease in seminal vesicles and prostate	-	X	X
Decrease in uterus	-	X	X

30-DAY ORAL TOXICITY IN THE RAT

Ref. AL 34

		DOSES MG/KG/DAY 8	40	200
HISTOPATHOLOGY				
Liver:	perilobular fatty infiltration (F)	-	-	10
Adrenals:	slight hyperplasia of the cells of the zona fasciculata (F)	-	-	2
Thyroids:	hyperactivity (M,F)	-	-	18
Ovaries:	folliculinic cysts	-	5	3
Uterus/vagina:	in oestrus	9	10	10
Mammary glands:	secreting	4	9	8
Seminal vesicles and prostate:	atrophy of epithelium	-	-	10

TEST COMPOUND: RU 38486

26-WEEK ORAL STUDY IN THE RAT

Ref. RSL 613/84260

SPECIES + STRAIN	NUMBER OF ANIMALS + SEX/GROUP	DURATION	ROUTE OF ADMINISTRATION	DOSAGE FORM	DOSE + FREQUENCY
Sprague-Dawley CD1 Rat	20 males (M) 10 females (F) per dose	26 weeks	oral, gastric tube	Micronised powder in suspension in an aqueous solution of 1% methycellulose	0.5 mg/kg/day 25 mg/kg/day 125 mg/kg/day Once daily

RESULTS: see following pages.

Mortality: (due to anaesthesia for blood sample)
1 female control
1 female receiving 125 mg/kg.

The incidents reported are considered to be attributable to treatment
(the figures refer to the number of animals concerned).

26-WEEK ORAL STUDY IN THE RAT

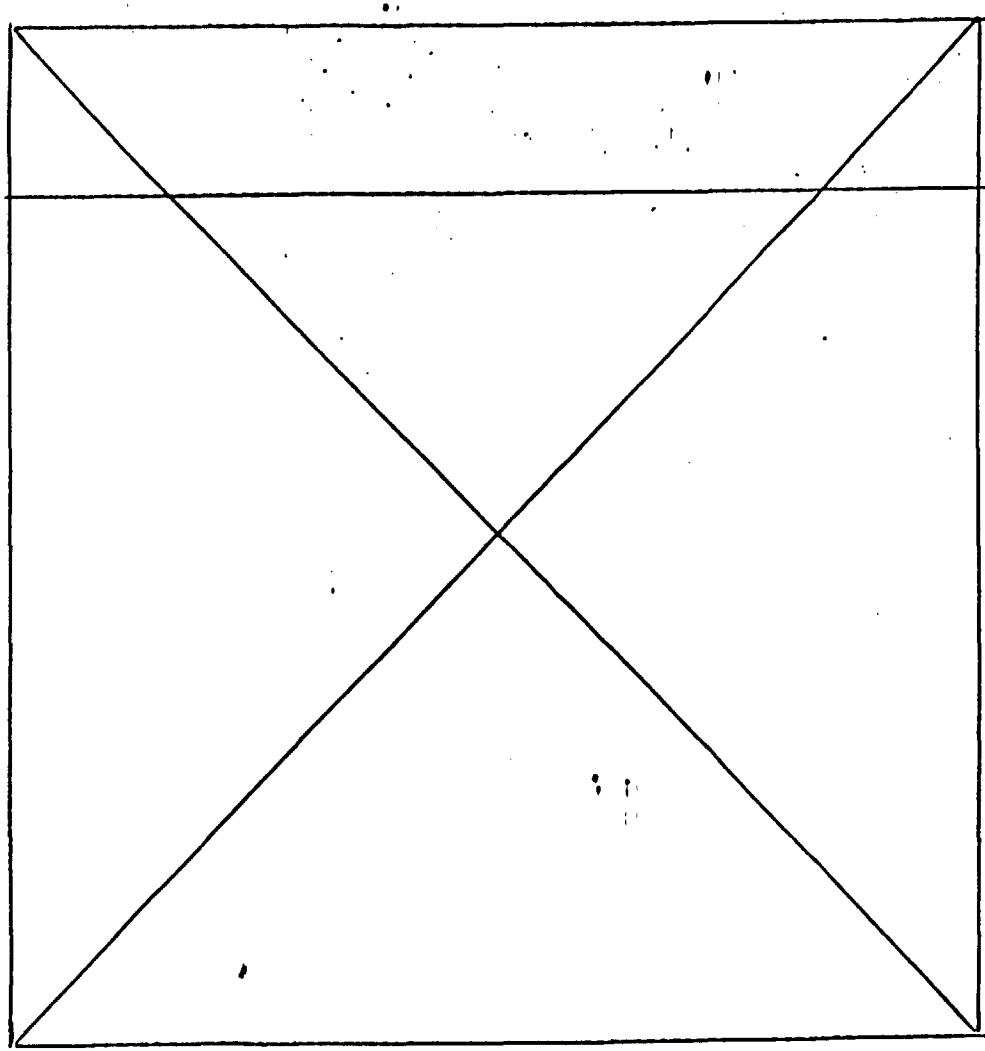
Ref. — RSL 613/84260

	DOSES MG/KG/DAY		
	5	25	125
BIOCHEMISTRY			
Decrease in glucose (F)	X	X	X
Increase in total proteins (M,F)	X	X	X
Increase in cholesterol (M,F)	–	X	X
Decrease in triglycerides (M,F)	X	–	X
Increase in phospholipids (M,F)	X	X	X
Increase in corticosterone (M,F)	–	–	X
Slight decrease in oestradiol	–	X	X
Decrease in ACTH (F)	–	X	X
Increase in progesterone	X	X	X
URINALYSES			
Proteinuria (M,F)	X	X	X
Increase in diuresis (M,F)	–	X	X
Increase in acidity (M,F)	X	X	X
HAEMATOLOGY			
Decrease in Hb, Hct, RBC (F)	–	X	X
Increase in platelets (F)	X	X	X
Decrease in prothrombin time (M,F)	–	–	X
Slight increase in WBC (F)	–	–	X

	DOSES MG/KG/DAY		
	5	25	125
BEHAVIOUR			
Hypersalivation (M,F)	–	X	X
Distension and pink colouration of the urogenital region (F)	X	X	X
Depression of weight gain (M)	–	X	X
Increase in food and water consumption (F)	X	X	X
Prolonged presence of keratinised cells in the vaginal smears	X	X	X
Decrease in heart rate (F)	–	X	X
MACROSCOPIC EXAMINATION			
Thickening of the mammary glands (F)	X	X	X
Hypertrophy of the pituitary (F)	X	X	X
Increase in adrenals (F)	–	X	X
Increase in thyroids (M,F)	X	–	X
Decrease in testes	–	–	X

26-WEEK ORAL STUDY IN THE RAT

Ref. RSL 613/84260



		DOSES MG/KG/DAY		
		5	25	125
ORGAN WEIGHTS				
Increase in pituitary (F)		X	X	X
Increase in adrenals (F)		-	X	X
Increase in thyroids (M,F)		X	X	X
Increase in liver (M,F)		X	X	X
Increase in kidneys (M,F)		-	X	X
Decrease in prostate and seminal vesicles		X	X	X
Decrease in testes		-	-	X
Decrease in uterus		X	X	X
HISTOPATHOLOGICAL EXAMINATION				
Thymus:	premature involution (M,F)	2	6	7
Liver:	minimal hypertrophy of centrilobular hepatocytes (M,F)	-	9	34
Spleen:	increase in the incidence of haemosiderosis (M,F)	7	9	15

INTRODUCTION

At the request of the ROUSSEL-UCLAF Medical Direction, we studied the acute oral toxicity in the Mouse of RU 38486 (micronized and non micronized forms).

RU 38486 was delivered by the "Département Central Produits", Romainville Research Centre, with the following references :

- micronized : batch No 8
- non micronized : batch No 6

EXPERIMENTAL PROTOCOL

(Following the recommendations of the Proposed Guidelines published by the Environmental Protection Agency of the United States of America in Federal Register, August 22nd, 1978).

1. Test animals

. Species

Male and female CD1 Swiss Mouse, Specific Pathogen Free, weighing between 17 and 20 g.

. Number of animals : 10 of each sex per dose.

The animals were marked with a 2 % phenol gentian violet aqueous solution as follows : head (T), back (D),tail (Q), head-back (TD), head-tail (TQ), head-back-tail (TDQ), right anterior leg (AD), left anterior leg (AG), right posterior leg (PD), left posterior leg (PG).

. Accommodation and diet

Mice were housed in groups of 10, all of one sex, in plastic cages measuring 335 x 190 x 130 mm. The litter (sterilized sawdust) was changed every day and animals were put in a clean cage every week.

The local was air-conditioned (temperature 21 + 1°C). The relative humidity was maintained within a range of 45 to 55 per cent. A time-controlled lighting syst was used to provide a regular lighting cycle (12 hours light, 12 hours dark).

Food was provided "ad libitum" in the form of pellets for rodents reference B 04).

Water was provided "ad libitum" in glass bottles changed every day.

2. Procedure

. Administration of test compound

All animals were dosed by gavage with an oesophageal tube. RU 38486 was dispersed in 0.25 % sodium carboxymethylcellulose with 0.2 % polysorbate 80. The volume administered was constant and equal to 20 ml per kg bodyweight. A control group received the vehicle alone under the same volume.

. Duration of study

The animals were observed for 21 days after dosing.

. Experimental design

a) Fasting : Food was withheld from animals the night prior to dosing and was given back 4 hours after the administration of the test compound.

b) Observations : The animals were observed frequently during the day of dosing and checked once each morning and late afternoon thereafter except during weekends and bank holidays (on these days, mortality was noted in the morning). The following was recorded : nature, onset, severity and duration of all gross or visible toxic or pharmacological effects (abnormal or unusual) on cardiovascular, respiratory, excretory, behavioural or other activity, as well as signs indicating an adverse effect on the central nervous system (paralysis, lack of coordination, staggering), pupillary reaction and time of death.

The weight of each animal was determined on the day of dosing, weekly thereafter or at death.

c) Sacrifice and autopsy : All test animals surviving at the end of the observation period were sacrificed. All test animals, whether dying during the test or sacrificed at the termination of the study, were subjected to a complete gross necropsy. All abnormalities were recorded.

If necropsy could not be performed immediately after a dead animal was discovered, the animal was refrigerated or frozen (during weekends) to minimize autolysis.

PROTOCOL

Animals	80 CD1, EOPS* Sprague Dawley rats (40 males and 40 females)
Source	[redacted]
Date of receipt	June 11, 1981 (male animals) and June 18, 1981 (female animals)
Acclimatization period	Ten days for the animals to get used to their new environment. Daily monitoring of the animals is carried out.
Housing	Five rats from the same group are placed in Dacron cages (dimensions: 400 x 320 x 150 mm). The litter (autoclaved wood shavings) is changed every day and the animals are placed in new cages every week. The room is air-conditioned (temperature 21 ± 1°C), with overpressure of air; the relative humidity is 50 ± 5%; the lighting is artificial and has a duration of 12 hours.
Feed	The rats receive feed in the form of standard reference B.04, granules (composition given in Appendix), given "ad libitum".
Water	The water is provided "ad libitum" in glass bottles which are changed daily.

* EOPS: Free from specific pathogens

A P P E N D I X I I

PROTOCOL

CASE RECORD FORM

LABORATORY DATA PARAMETERS

PROTOCOL

STUDY OF TOLERABILITY OF SINGLE DOSES OF RU 486 IN HEALTHY FEMALE VOLUNTEERS

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1. INTRODUCTION

1.1 Product description

RU 486 is an anti-progesterone and anti-glucocorticoid steroid synthesized by Roussel UCLAF. It is an 11-beta substituted 19-norsteroid.

Pharmacokinetics of tritiated RU 486 have been studied after I.V. administration of a tracer dose (280 mg, 25 µCi) and after oral administration of a pharmacologically active dose (100 mg, 50 µCi). In both cases the plasma kinetic curves correspond to an open two-compartment model. After I.V. administration, $t\frac{1}{2}$ distribution = 1 hr, $t\frac{1}{2}$ elimination = 12 hrs; volumes of distribution are very low, Vc = 8 ℓ and Vd ss = 26 ℓ. After oral administration, $t\frac{1}{2}$ distribution = 1 hr and $t\frac{1}{2}$ elimination = 24 hrs; volumes of distribution are higher than previously, Vc, = 45 ℓ and Vd ss = 100 ℓ. The maximum plasma concentration of RU 486, about 2% of the administered dose per liter, is observed one hour after intake of the tablets.

Urinary and fecal excretion reach completion in 6 days and 9% of the administered radioactivity is excreted in urine whatever the route of administration. RU 486 seems to be well absorbed (tmax = 1 h and same urinary excretion of radioactivity after I.V. or oral route), however the absolute bioavailability calculated from AUCs is 30 to 50%. This appears to be due to a first pass effect as the Cmax of RU 42633, the N monodemethyl metabolite of RU 486, is observed 1-2 hrs after oral administration and 9 h after I.V. administration. Moreover the AUCs of RU 42633 are higher after oral administration than after I.V. administration.

Further information is available in the Investigator's Brochure.

1.2 Aim of the study

To study the tolerability of the drug in healthy female subjects in doses ranging from 200 to 2 000 mg.

The trial will be performed at the Clinical Pharmacology Unit, Department of Pharmacology,

2. STUDY DESCRIPTION

- Open study
- Independent groups of 4 subjects for each dose
- Administration of increasing doses
- After administration of each dose, the occurence of unusual symptoms, the results of blood pressure and pulse measurements, Hematology, Clinical Chemistry and urinalysis will be taken into account when deciding whether to proceed to the next higher dose. Should any clinically significant effect(s) be noted, the next higher dose will not be administrated and the tolerability study terminated. Hormone plasma levels will not serve as additional indication of whether to proceed with the next higher dose.
- If an undesirable effect appears which may be considered by the investigator as a chance occurrence, the same dose will be repeated in 4 new subjects in a cross-over randomized study versus placebo. If this effect is confirmed but not considered severe enough to stop the study, a smaller increment than what was originally planned may be used for the next dose. This increment will be defined jointly with Roussel UCALF.

3. SELECTION OF STUDY POPULATION

3.1 Inclusion criteria

Subject must meet the following criteria:

a. Females 18 and 45 years of age
b. Body weight not more than 10% above or below their ideal weights for heights and ages
c. Normal findings in the physical examination
d. Normal laboratory values (unless the investigator considers an abnormality clinically unimportant)
e. Normal ECG and vital signs
f. Normal chest X-ray
g. Normal gynecological history
h. No possibility of pregnancy:

(i) intra uterine device inserted at least 6 months, but not more than 2 years before commencement of the study.
or (ii) tubal sterilisation
or (iii) sterile partner or no partner

3.2 Exclusion criteria

a. Regular use of medication, abuse of alcoholic beverages, or participation in a trial with an investigational drug in the 4 weeks preceding the study.
b. Treatment within the previous three months with any drug known to have a well defined potential for toxicity to a major organ (e.g. chloramphenicol).
c. A clinically important illness during the 4 weeks preceding the study.
d. History of hypersensitivity to any drug.
e. History or presence of gastrointestinal, liver or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or of lasting gynecological disorders.

3.3 Subject recruitment

Population from which sample is drawn: Healthy female volunteers of the population of

3.4 Subject numbers

3.4.1 Number per treatment group: 4.
3.4.2 Total subject number: 24 subjects if all doses are well tolerated.

4. DRUG ADMINISTRATION

4.1 Drug dosage

4.1.1 Test drug: RU 486 - Scored tablets of 50 mg.
Increasing single doses of 200, 400, 800, 1200, 1600 and 2000 mg will be administered to four new volunteers for each dose, on a weekly basis, provided that the last dose has been tolerated.

4.1.2 Placebo tablets (see paragraph 2).

4.1.3 Dosage schedule and route of administration.

Each dose will be administered orally in one single intake, with 500 ml of water over 5 minutes, at 07h30 a.m., after an overnight fasting period of at least twelve hours.

4.2 **Drug Supplies**

4.2.1 RU 486 verum and placebo tablets will be prepared by the Pharmaceutical Department, at Roussel UCLAF.

4.2.2 Packaging and labelling:
Tablets will be packed in bottles of 200 tablets corresponding to — Tablets of RU 486 verum and — Tablets of RU 486 placebo.

Eventual randomisation (see paragraph 2) and individual packaging will be performed at ———

The bottles will carry the following information:

* Number of tablets
* Product identification

  RU 486 50 mg tablets

  or

  RU 486 placebo tablets
* Batch number.

4.3 **Assignment of study medication**

The investigator will be responsible for safe keeping of the study drug. It will be stored according to the prescribed conditions in the Pharmacology Unit, separate from other medicaments.

4.4 Concurrent treatments

4.4.1 Any treatment is forbidden during the study.

4.4.2 Statement 4.4.1 is not valid if the use of drugs becomes necessary to protect the health of the subject, because of the occurrence of a pathological event whether this event is due to RU 486 or not.

5. CRITERIA OF EVALUATION METHODS

5.1 Clinical criteria

* Medical history and physical examination
* Weight
* Vital signs (supine and standing radial pulse rate, respiratory rate, temperature and supine and standing blood pressure)

5.2 Laboratory examinations

* Hematological status (hemoglobin, hematocrit, RBC, WBC and differential count, platelet count) and hemostasis parameters (fibrinogenemia, partial thromboplastin time, specific assay of factors X, VII, V, II, euglobulins lysis time)
* Clinical chemistry (glucose, total protein, albumin, globulin, A/G ratio, BUN, creatinine, total bilirubin, alkaline phosphatase, ASAT, ALAT, LDH, calcium, inorganic phosphorus, uric acid, sodium, potassium, chloride, cholesterol, triglycerides, CPK).
* Urinalysis (colour, pH of freshly voided specimens, specific gravity, protein, glucose, ketones, blood and microscopic sediment)

5.3 Hormone examinations

* ACTH
* Cortisol

measured at 07h30 a.m.

5.4 Other parameters

5.4.1 Before and 2 hours, 24 hours, 48 hours and 8 days after drug intake: electrocardiogram (standard 12-lead)

5.4.2 Assay of RU 486 in plasma. 10 ml of blood will be taken 24 hours after drug intake. Frozen plasma will be kept in [redacted] then forwarded to Roussel Uclaf for assay of RU 486.

5.5 Recording of side effects

Before commencement of each phase of the study, each subject will receive a form into which all side effects should be entered hourly up to 6 hours and thereafter 3-hourly up to 36 hours, after medication (except when asleep). As from 12 hours onwards, side effect forms may be completed at home by volunteers.

All adverse events occurring during the study must be reported in the Case Report Form. A serious life threatening adverse event and/or death due to any cause occurring in a subject participating in this study should be immediately reported to Roussel Uclaf.

6. COURSE OF THE STUDY

6.1 Pretreatment observations and investigations

The subject will be screened within two weeks before drug administration for their fitness to participate. This screening will include:

* Clinical examinations listed in paragraph 5.1 and recording of height and weight.
* Electrocardiogram (standard 12 lead).
* Chest X-ray if not taken within the last 6 months.

6.2 RU 486 will only be administered on the 2 days preceding the expected menstrual period or the 4 days following the onset thereof.

6.3 Observations and investigations just before and after dosing

* Subjects will be under monitoring by the Pharmacology Unit for 36 hours. Subsequently, they will have to come for a morning visit at day 3, 4, 6 and 8. Volunteers must be aware that any kind of stress must be prohibited before coming to the unit.
* In each case the dose of RU 486 will be administered orally with 500 ml water over 5 minutes at 07.30 a.m.
* The day of administration is called day 1.
* Before commencement of each phase of the study, each subject will receive a form into which all side-effects should be entered hourly up to 6 hours and thereafter 3-hourly up to 36 hours, after medication (except when asleep). As from 12 hours onwards, side-effect forms may be completed at home by volunteers.
* Any mentrual abnormalities (next menses included) or intermentrual bleeding will be reported.
* Blood pressure, respiratory rate and pulse rate (see paragraph 5.1) will be measured before medication and $\frac{1}{2}$ hourly up to 3 hours post medication. Thereafter these parameters will be measured hourly up to 6 hours after medication and 12, 24, 48 and 72 hours after medication.
* Body temperature will be recorded before medication, 4 and 12 hours after medication, then daily in the morning throughout the study.
* Electrocardiogram will be recorded before and two hours, 24 hours, 48 hours and 8 days after medication.
* Laboratory examinations as listed under paragraph 5.2 will be performed just before and 6 hours, 24 hours and 7 days after drug administration. **If a laboratory parameter appears to be abnormal on the 7th-day examination, this parameter will be checked weekly until returned to normal.**
* ACTH and cortisol will be measured before dosing and at day 2, 3, 4, 6 and 8 at 7.30 a.m. Hormone assays will be performed altogether in one set at the end of the study.
* All laboratory examinations including hormone assays will be performed in the _____

Blood sampling (10 ml) for assay of RU 486 will take place 24 hours after drug intake.

8. PROTOCOL DEVIATIONS AND AMENDMENTS

Protocol deviations and amendments, if any, will be dated and described as an appendix to this protocol. (See also paragraph 2).

There will be no alteration of the protocol without the express written approval of Roussel Uclaf.

9. SUBJECT DROPOUTS AND WITHDRAWALS

All reasons for drop-outs and withdrawals will be carefully noted in the Case Report Forms.

These subjects will be replaced unless withdrawal is due to an event giving evidence of a major toxicity of the compound. Such an event would lead to stop the study.

10. BIOMETRICS

* Case Report Forms will be checked as soon as completed for corrections and completeness by the investigator.
* Incomplete observations of drop-outs and withdrawals will be taken into account for the analysis.

11. PLANNING

11.1 Agreements and consents

11.1.1 Ethical Committee

In accordance to Government regulations, the appropriate Ethical Committee or Institutional Review Board must review and approve this protocol.

11.1.2 Informed consent of subjects

All subjects will give their written informed consent prior to commencement of the study. It will be made clear to the subjects that they have the right to discontinue their participation at any time and without explaining the reasons why.

11.1.3 Confidentiality

All data are the property of Roussel UCLAF and must not be communicated to third parties without the express written permission of Direction Médicale Roussel Uclaf.

11.1.4 Publication

The results of this study are not intended for publication.

11.1.5 In performing this study, both the investigator and the sponsor endorse, as a minimum, the standards for conduct of Clinical Research activities as set forth in the Declaration of Helsinki.

11.2 **Time Table**

11.2.1 Duration of study: Ca 3 months.

11.2.2 Target dates: Start: Q4 1984
Finish: Q1 1985
Report: After statistical analysis is available.

11.3 **Study monitoring by Roussel Uclaf**

This study will be monitored by Roussel UCLAF Clinical Research personnel at regular stages of its development by personal visits and telephone communications.

11.4 **Study termination**

At the end of the study, the remaining unutilised tablets will be forwarded back to Roussel UCLAF.

11.5 Signature of Chief Investigators

B H Meyer

PROF. B.H. MEYER

12 10 84

BLOEMFONTEIN

Dec 30, 1984

ROMAINVILLE

DIRECTION MEDICALE ROUSSEL-UCLAF
102, route de Noisy
93230 ROMAINVILLE
TEL. [illegible]

APPENDIX 1

AMENDMENT TO THE PROTOCOL

Course of the study :

RU 38.486 will only be administered on day 1, 2 or 3 of a menstrual period.

CASE RECORD FORM

Study number: ZA/84/486/05

STUDY OF TOLERABILITY OF SINGLE DOSES OF RU 486 IN HEALTHY FEMALE VOLUNTEERS

Trial conducted in Clinical Pharmacology Research Unit,
Department of Pharmacology,

Subject: Surname:

Name:

Initials:

Dose of RU 486 administered (mg) [ ]

Subject Number: [01]

PATIENT IDENTIFICATION:

Surname: _____ Name: _____

Sex: _____ Weight (kg): _____

Height (cm): _____ Age (years): _____

Occupation: _____

CONSENT OBTAINED?

Yes [ ]

TOBACCO CONSUMPTION:

None [ ] Cigarettes [ ] Cigars [ ] Pipe [ ]

Quantity per day: ____ ____ ____

ALCOHOL CONSUMPTION:

None [ ] Beer [ ] Wine [ ] Hard liquor [ ]

Quantity per day: ____ ____ ____

DRUG CONSUMPTION (REGULAR)

None [ ]

Medication: 1. ..... 2. .....

Daily dose: ....

Date started: ....

Date completed: ....

DRUG CONSUMPTION (OCCASIONAL)

None [ ]

Medication: 1. ..... 2. .....

Daily dose: ....

Date started: ....

Date completed: ....

Surname of subject: ..... Subject Number: [ ]

PARTICIPATION IN TRIAL WITH INVESTIGATIONAL DRUG:

Yes [ ] No [ ]

If yes, date of last trial: .....

drug involved: .....

HISTORY OF ALLERGY:

Yes [ ] No [ ]

If yes, details: .....

HISTORY OF HYPERSENSITIVITY TO DRUGS:

Yes [ ] No [ ]

If yes, details: .....

HISTORY OF DISEASE:

Yes [ ] No [ ]

If yes, details: .....

HISTORY OF SURGERY:

Yes [ ] No [ ]

If yes, details: .....

COMMENTS:

INVESTIGATOR'S SIGNATURE:

Surname of subject: ..... Subject Number: [ ]

Date of examination: ....

PHYSICAL EXAMINATION BEFORE TRIAL

Pulse rate (beats/minute) (supine): .....

Blood pressure (mmHg) (supine): systolic: .....

diastolic: .....

	Normal	Abnormal	Not done	Comments
Head + neck	[ ]	[ ]	[ ]	.....
Eyes	[ ]	[ ]	[ ]	.....
Ears	[ ]	[ ]	[ ]	.....
Nose	[ ]	[ ]	[ ]	.....
Throat	[ ]	[ ]	[ ]	.....
Lungs	[ ]	[ ]	[ ]	.....
Heart	[ ]	[ ]	[ ]	.....
Breasts	[ ]	[ ]	[ ]	.....
Abdomen	[ ]	[ ]	[ ]	.....
Extremities	[ ]	[ ]	[ ]	.....
Lymph nodes	[ ]	[ ]	[ ]	.....
Skin	[ ]	[ ]	[ ]	.....
ECG	[ ]	[ ]	[ ]	.....

ADDITIONAL COMMENTS:

INVESTIGATOR'S SIGNATURE:

Surname of subject: ..... Subject Number: _[ ]

CLINICAL EXAMINATION

	Before medication	6 Hours after medication	24 Hours after medication
Head + neck	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Eyes	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Ears	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Nose	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Throat	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Lungs	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Heart	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Breasts	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Abdomen	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Extremities	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Lymph nodes	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Skin	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
ECG	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]	norm. [ ] abn. [ ]
Weight (kg):	.....	.....	

COMMENTS:

INVESTIGATOR'S SIGNATURE

Surname of subject: ..... Subject Number: [ ]

HEMATOLOGY + URINALYSIS

	Before med.	6 hours after med.	24 hours after med.	168 hours after med.
Leucocytes				
R.B.C.				
Hemoglobin				
Hematocrit				
G.K.V.				
G.K.H.				
G.K.H.K.				
Platelets				
Sedimentation rate				
Reticulocytes				
Neutrophils				
Eosinophils				
Basophils				
Lymphocytes				
Monocytes				
Prothrombin time				
Fibrinogen				
Factor II				
Factor V				
Factor VII				
Factor X				
Euglobulin lysis time				

URINALYSIS:

pH				
S.G.				
Abnormalities				

Surname of subject: ..... Subject Number: [ ]

CLINICAL CHEMISTRY

	Before med.	6 hours after med.	24 hours after med.	168 hours after med.
Sodium				
Potassium				
Chloride				
CO_2				
Urea				
Creatinine				
Urate				
Calcium				
Phosphates				
Proteins				
Albumin				
Tot. Bilirubin				
Conj. Bilirubin				
ALP				
G-GT				
AST				
ALT				
LD				
Cholesterol				
Triglycerides				
Glucose				
CPK				

Study number: ZA/84/486/05

Surname of subject: .....

Subject Number: [ ]

CLINICAL CHEMISTRY

	Before med.	6 hours after med.	24 hours after med.	168 hours after med.
Sodium				
Potassium				
Chloride				
CO_2				
Urea				
Creatinine				
Urate				
Calcium				
Phosphates				
Proteins				
Albumin				
Tot. Bilirubin				
Conj. Bilirubin				
ALP				
G-GT				
AST				
ALT				
LD				
Cholesterol				
Triglycerides				
Glucose				
CPK				

Surname of subject: ..... Subject Number: [ ]

	ACTH (pg/mℓ)	CORTISOL (nmol/ℓ)	TESTOSTERONE (nmol/ℓ)
Before medication			
24 hrs. after medication			
48 hrs. after medication			
72 hrs. after medication			
120 hrs. after medication			
168 hrs. after medication			

ECG ABNORMALITIES

	NORMAL	ABNORMAL
Before medication	[ ]	[ ]
2 hrs. after medication	[ ]	[ ]
24 hrs. after medication	[ ]	[ ]
48 hrs. after medication	[ ]	[ ]
192 hrs. after medication	[ ]	[ ]

DESCRIPTION OF ABNORMALITIES:

INVESTIGATOR'S SIGNATURE.

Surname of subject: ..... Subject Number: [ ]

SIDE-EFFECTS

	NO	YES	IF YES, DETAILS
1 Hour after medication	[ ]	[ ]	
2 hours after medication	[ ]	[ ]	
3 hours after medication	[ ]	[ ]	
4 hours after medication	[ ]	[ ]	
5 hours after medication	[ ]	[ ]	
6 hours after medication	[ ]	[ ]	
9 hours after medication	[ ]	[ ]	
12 hours after medication	[ ]	[ ]	
15 hours after medication	[ ]	[ ]	
18 hours after medication	[ ]	[ ]	
21 hours after medication	[ ]	[ ]	
24 hours after medication	[ ]	[ ]	
27 hours after medication	[ ]	[ ]	
30 hours after medication	[ ]	[ ]	
33 hours after medication	[ ]	[ ]	
36 hours after medication	[ ]	[ ]	

COMMENTS:

INVESTIGATOR'S SIGNATURE:

Surname of subject: ..... Subject Number: [ ]

	Blood Pressure (mmHg)	Respiration rate/minute	Pulse rate beats/min.	Temperature (°C)
Before medication				
30 min. after med.				
1 hr. after med.				
1½ hr. after med.				
2 hrs. after med.				
2½ hrs. after med.				
3 hrs. after med.				
4 hrs. after med.				
5 hrs. after med.				
6 hrs. after med.				
12 hrs. after med.				
24 hrs. after med.				
48 hrs. after med.				
72 hrs. after med.				

COMMENTS:

INVESTIGATOR'S SIGNATURE

Surname of subject: ..... Subject Number: [ ]

DETAILS REGARDING CONTRACEPTION:

The following method is used:

1. Contraceptive tablet ("the pill") Yes/No
2. Injections Yes/No
3. Intra uterine device Yes/No
   If yes, date inserted: .....
4. Sterilization by tubal ligation Yes/No
5. Sterile husband/partner Yes/No
6. No partner Yes/No

MENSTRUAL HISTORY BEFORE TRIAL

1. First day of last menstrual period (date): .....
2. Normal duration of cycle (days): .....
3. Normal duration of menstruation (days): .....
4. Menstrual abnormalities: Describe: .....
   .....
5. Date of medication with RU 486: .....
6. Were you menstruating on this date? Yes/No
   If yes, date of commencement of menses: .....
7. Duration of menstrual period after medication (days): .....
8. Menstrual abnormalities after medication (describe): .....
   .....
9. Details regarding subsequent cycle: .....
   .....
10. Intermenstrual bleeding Yes/No
11. Date of commencement of subsequent menstrual period: .....
12. Abnormalities associated with subsequent menstrual period: .....
    .....

INVESTIGATOR'S SIGNATURE:

00202

Laboratory investigations :

Definition of normal laboratory range (N.L.R.), predefined changes (P.D.C.) and extended range

HEMATOLOGY

	Units	N.L.R.	P.D.C.	Extended range
Erythrocytes	mill/cmm	4.0 - 6.0	decrease of 1 mill	3.6 - 6.6
Hemoglogin	g/dl	12.5 - 16.5	decrease of 2 g	11.25 - 18.15
Hematocrit	%	37 - 47	decrease of 5 %	33 1/3 - 51.7
Mean corpuscular volume (MVC)	fl	80 - 100	-	-
Mean corpuscular hemoglobin (MCH)	pg	27 - 33	-	-
Mean corpuscular hemoglobin concentration (MCHC)	%	31 - 35	-	-
Reticulocytes	mill/cmm	0.01 - 0.1	-	-
E.S.R.	mm 1st hour	0 - 5	increase of 10 mm	0 - 10
Leucocytes	thous/cmm	3.5 - 12.5	decrease of 2 thous	2.6 - 15.2
Neutrophils	thous/cmm	1.8 - 7.5	decrease or increase of 2 thous	1.6 - 8.2
Eosinophils	thous/cmm	0.04 - 0.45	decrease or increase of 0.25 thous	0 - 0.9
Basophils	thous/cmm	0.01 - 0.10	decrease or increase of 0.24 thous	0 - 0.2
Lymphocytes	thous/cmm	1.50 - 4.90	decrease or increase of 1 thous	1.1 - 6.1
Monocytes	thous/cmm	0.2 - 0.80	decrease or increase of 0.4 thous	0.1 - 1.6
Platelets	thous/cmm	150 - 400	decrease of 100 thous	112 - 500

Laboratory investigations :

Definition of normal laboratory range (N.L.R.), predefined changes (P.D.C.) and extended range

BIOCHEMISTRY

	Units	N.L.R.	P.D.C.	Extended range
Sodium	mmol/l	136 - 147	increase or decrease of 8 mmol	-
Potassium	mmol/l	3.7 - 5.1	increase or decrease of 0.75 mmol	-
Chloride	mmol/l	98 - 108	increase or decrease of 5 mmol	-
Carbone dioxide	mmol/l	19 - 28	increase or decrease of 8 mmol	-
Urea	mmol/l	2.5 - 6.7	increase of 2.9 mmol	1.9 - 8.4
Creatinine	umol/l	60 - 110	increase of 40 umol	54 - 121
Urate	mmol/l	0.18 - 0.45	increase of 0.12 mmol	-
Calcium	mmol/l	2.20 - 2.60	increase or decrease of 0.5 mmol	1.9 - 2.9
Phosphate	mmol/l	0.80 - 1.45	increase or decrease of 0.43 mmol	0.7 - 1.6
Proteins	g/l	65 - 80	increase or decrease of 15 g	58 - 88
Albumin	g/l	38 - 52	increase or decrease of 7.5 g	34 - 57
Total bilirubin	umol/l	4 - 21	increase or decrease of 8 umol	2 - 31
Conjugated bilirubin	umol/l	1 - 4	-	-
Cholesterol	mmol/l	3.9 - 6.5	increase or decrease of 2 mmol	3.51 - 7.15
Glucose	mmol/l	3.6 - 5.8	increase or decrease of 1.5 mmol	2.7 - 7.2
Triglycerides	mmol/l	0 - 1.7	increase of 0.85 mmol/l	0 - 2

Laboratory investigations :

Definition of normal laboratory range (N.L.R.), predefined changes (P.D.C.) and extended range

	Units	N.L.R.	P.D.C.	Extended range
COAGULATION TESTS				
Prothrombine time	%	80 - 100	decrease or increase of 20 %	72 - 110
Fibrinogen	mg/l	150 - 400	-	-
Factor II	%	50 - 150	-	-
Factor V	%	50 - 150	-	-
Factor VII	%	50 - 150	-	-
Factor X	%	50 - 150	-	-
Euglobulin lysis time	Sec.	60	-	-
URINALYSIS				
pH	-	4.6 - 8	-	-
specific gravity	-	1005 - 1030	-	-
ENZYMOLOGY				
Alkaline phosphatase	IU/l	25 - 100	increase of 100 IU	19 - 125
GT	IU/l	5 - 65	increase of 65 IU	0 - 130
A.S.A.T.	IU/l	5 - 40	increase of 40 IU	0 - 80
A.L.A.T.	IU/l	5 - 35	increase of 35 IU	0 - 70
L.D.H.	IU/l	100 - 350	increase of 350 IU	90 - 385
C.P.K.	IU/l	15 - 130	increase of 130 IU	12 - 156

APPENDIX I

- Protocol
- Case record form
- Randomisation

INHIBITION BY RU 38486 OF THE ACUTE EFFECT OF DEXAMETHASONE ON CIRCULATING LEUCOCYTES IN NORMAL SUBJECTS

RU 38486 is an original compound synthesised in the Roussel-Uclaf Research Department which has been shown in hormone receptor binding and animal pharmacology studies to be antiprogesterone, antiglucocorticoid and weakly anti-androgenic without possessing any agonist properties (1).

An initial clinical pharmacology study in a single dose showed that the administered doses (50 to 400 mg) were very well tolerated in clinical and biochemical terms and that from at doses of 200 mg and above RU 38486 administered at 2 a.m. caused a significantly greater rise in cortisol and LPH levels than after placebo between 7 and 11 a.m.

This increase in cortisol and LPH levels is interpreted as an effect of the antiglucocorticoid action of the compound at the pituitary level. It is the simplest action to demonstrate after a single dose of compound.

A second study demonstrated that RU 38486 inhibited the plasma suppression induced by administration of dexamethasone with a dose-response effect.

In order to test for a peripheral antiglucocorticoid effect of RU 38486, the variations in the differential leucocyte count will be studied under the effect of dexamethasone with and without the test compound. Preliminary studies have suggested a correction of dexamethasone-induced leucocytic variations by RU.

1. AIM

To study the effect of 400 mg RU 38486 administered in a single dose at 8 a.m. on the action of dexamethasone on circulating white blood cells.

2. STUDY SCHEDULE

2.1. Double-blind study in 8 subjects divided into 2 latin squares receiving successively at an interval of one week one of the following four treatments:

- Placebo + placebo
- Placebo + dexamethasone
- RU 38486 + placebo
- RU 38486 + dexamethasone

2.2. The subjects will receive 8 tablets at 8 a.m., each containing 0 or 50 mg of active substance (i.e. 0 or 400 mg RU 38486) and 1 hour later 2 tablets each containing 0 or 0.5 mg dexamethasone (Dectancyl) (0 or 1 mg dexamethasone in total).

2.3. The constitution of the 2 latin squares with the allocation of the successive treatments for each subject will be done by Roussel-Uclaf.

3. SUBJECT SELECTION

3.1. Eight subjects will participate in the study.

3.2. Inclusion criteria

i) Subjects must be male.

ii) Subjects must be aged from 18 to 40 years.

iii) The subjects' weight must not deviate by more than ± 10% from the ideal weight for their age and height.

iv) Subjects must have undergone a clinical and laboratory examination confirming the absence of any abnomalities.

3.3. Exclusion criteria

i) Subjects with a history of allergy or hypersensitivity to medication.

ii) Subjects regularly taking drugs or having received within the 3 months prior to this study a drug known to be toxic (cf. chloramphenicol) or eliminated very slowly from the body.

iii) Subjects drinking alcohol or smoking to excess.

iv) Subjects suffering from a serious acute disease in the month prior to the study.

v) A history of gastro-intestinal, hepatic or renal disease likely to interfere with the absorption, metabolism or excretion of the compound.

4. STUDY PROCEDURE

4.1. Examination for inclusion in the study

Clinical examination.
Haematological and biochemical examination.

4.2. Diet

Subjects will follow their normal diet.

4.3. Alcohol and drugs

Subjects must abstain from alcohol 24 hours before each administration of compound until the end of each test.

No medication may be taken during the 8 days prior to the study and throughout its duration.

4.4. Procedure for each test

At 8 a.m. = sample for complete blood count and hormone assays.

Followed immediately afterwards by administration of 400 mg RU 38486 or placebo.

At 9 a.m. = administration of 1 mg Dectancyl or placebo.

At 3 p.m. = complete blood count and hormone assays,

During the test the subjects will pursue their normal activities.

5. TEST COMPOUNDS

5.1. Dexamethasone (Dectancyl) or placebo will be administered in a single dose in the form of identical tablets each containing 0 or 0.5 mg of active compound, presented in bottles containing 2 tablets labelled with the week number and the subject's number, the randomisation for which is undertaken by Roussel-Uclaf.

5.2. RU 38486 or placebo will be supplied by the Roussel-Uclaf pharmaceutical department in the form of identical tablets each containing 0 or 50 mg of active ingredient presented in a bottle of 8 tablets labelled with the subject's number and that of the week.

5.3. For each of the 8 subjects, the 4 bottles of Dectancyl or placebo and the 4 bottles of RU or placebo necessary for the whole study will be prepared in advance, but supplied by unit for each week.

6. ASSESSMENT CRITERIA

Hormone assays: cortisol, LPH, ACTH.

Differential leucocyte count: neutrophils, basophils, eosinophils, monocytes, lymphocytes.

7. ACTION TO BE TAKEN IN THE EVENT OF INTOLERANCE

Subjects are free to withdraw from the study at any time.

In the event of unusual signs or symptoms, the investigator will take the measures he considers necessary.

8. ASSAYS, PRACTICAL MEASURES

The complete blood counts will be done in the [redacted] The hormone assays (cortisol, LPH, ACTH) will be done at

9. STATISTICAL ANALYSIS

The analysis of the results (curves and analyses of variance) will be done in the Roussel-Uclaf Biometry Department.

Electronic Mail Message

Date: 2/24/95 4:16:00 PM
From: [redacted]
Subject: RU-486 Availability

I confirmed with Sandra Waldman, public information contact for US Population Council in NY, that they have received requests for RU-486 for studies and have not responded to meet the requests for two reasons. Most importantly, Roussel Uclaf has not given them a supply of drug when they donated the US rights to them in 1993 and continue to decline to do so; and secondly, the Population Council is not set up to review and prioritize these requests. The Council is in negotiations with manufacturers but Ms. Waldman has no idea when an agreement will be reached--"few months to a year."

We have not been aware of a drug shortage problem:
1. The Agency's compassionate release program has not been affected since Roussel-Uclaf continues to supply drug directly for this indication.
2. The only clinical trial the Agency has had the opportunity to review and approve after the donation of rights to the Population Council was a

[redacted]

I have a call into our contact at Roussel-Uclaf but was unable to reach him today because of time differences.

[redacted]

APPEARS THIS WAY
ON ORIGINAL

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

Date: 24-Feb-1995 03:59pm EST
From: [redacted]

Dept: HFD-150 WOC2
Tel No: [redacted] FAX 301-594-0499

TO: [redacted]

Subject: RU-486 Availability

I confirmed with Sandra Waldman, public information contact for US Population Council in NY, that they have received requests for RU-486 for studies and have not been able to meet the requests for two reasons. Most importantly, Roussel Uclaf did not give them a supply of drug when they donated the US rights to them in 5/94 and continue to decline to do so; and secondly, the Population Council is not set up to review and prioritize these requests. The Council is in negotiations with manufacturers but Ms. Waldman has no idea when an agreement will be reached--"few months to a year."

We have not been aware of a drug shortage problem:

1. The Agency's compassionate release program has not been affected since Roussel-Uclaf continues to supply drug directly for this indication.
2. The only clinical trial the Agency has had the opportunity to review (and approve) after the donation of rights to the Population Council was [redacted]

I have a call into our contact at Roussel-Uclaf but was unable to reach him today because of time differences.

[redacted]

Mifepristone
Abortion Rights Mobilization (A.R.M.)
Lawrence Lader

December 6, 1993

Memorandum of Meeting

A.R.M. Representatives:
Lawrence Lader, President
David Horn, Ph.D., Columbia University (Consultant)

Purpose: This pre-IND meeting was requested by Mr. Lader to discuss the regulatory process to develop a non-French mifepristone under an IND sponsored by A.R.M.

Discussion and Conclusions:

Mr. Lader thanked the Division for meeting with him and Dr. Horn. He indicated that his organization believes that negotiations between the Population Council and Roussel Uclaf will not result in clinical trial for RU-486. Therefore, his organization, A.R.M. would like to pursue an IND for clinical development of their mifepristone. He further indicated that the Population Council has given him right of reference to their IND for mifepristone; however, Roussel Uclaf has not provided authorization to cross-reference the data (toxicology and chemistry, manufacturing and controls (CMC)) under the Population Council's application.

The discussion initially focused on the issue of bioequivalence and the lack of access to the Roussel Uclaf data. indicated that the Division could not accept a paper NDA without access to the case report forms on the individual patients tested in the Roussel clinical trials. Typically, a paper NDA is submitted after a full new drug application for a similar product has been reviewed and approved by FDA. Under this situation, FDA has reviewed the clinical data submitted by literature reference and bioequivalence data would be the primary requirement for the paper NDA. stated that mifepristone is not yet approved in the U.S., and unless Roussel Uclaf provided FDA with the clinical data, a paper NDA would probably not be possible. Even if Roussel provided a right of reference to their clinical data, the issue still remains that mifepristone is not approved in the U.S. Therefore, bioequivalence would not be a relevant issue in this situation.

further indicated that unless A.R.M. received authorization to cross-reference Roussel's toxicology data and CMC information, they would be required to conduct toxicology testing and provide the CMCs.

suggested that A.R.M. proceed as though the Population Council IND never existed.

The Division explained what information would be required to submit an IND to begin clinical testing:

1. Toxicology data to include (1) acute testing in rats and dogs, (2) repeat administration, 1 to 2 weeks in duration, and (3) teratology profile.

2. Chemistry, manufacturing and control information for the drug substance and product, including the clinical batches.

3. Clinical protocol, including sample size and proposed statistical analysis.

The Division indicated that the preclinical testing should be complete prior to initiating the clinical trials. ——— will provide ———with the necessary forms and instruction for the IND.

Mr. Lader suggested that his organization has found a manufacturing facility interested in manufacturing the mifepristone for both the clinical trials and a marketed product. Mr. Lader intends to meet with the Population Council to discuss these issues and a possible joint venture into the experimental testing of their product.

informed Mr. Lader that FDA would not involve itself with the legal issues associated with the patent held by Roussel Uclaf on mifepristone. Mr. Lader assured the Division that his lawyers are researching the patent laws and the investigational use of their mifepristone would not infringe on the patent; however, an attempt to market their mifepristone would result in a patent infringement.

/S/

——— CSO

cc: HFD-510/UTERINE ACTING AGENTS
Attendees

HFD ———
HFD- ——— 12/7/93/ — 003/ft/sno/2/16/94
concurrence: ——— /1/3/ ——— 1/4/ ——— /1/5/94

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

I N T E R O F F I C E M E M O R A N D U M

TO: See Below

Subject: Pre-IND RU-486\Larry Lader

NOTICE OF FORTHCOMING MEETING

DATE: Thursday, March 31, 1994
TIME: 10:00 AM - 11:00 AM
PLACE: C\R 13B-39

Purpose: Dr. Lader is initiating pre-IND studies usung RU-486 imported from the United Kingdom. The Division suggested this meeting to discuss protocol for pre-clinical studies as well as projections for clinical studies.

Background: Dr. Lader has already gained media coverage for his clinical studies on RU-486. He intends to import ———— of the drug from either ———— or ———— in the UK. This he plans to use for both pre-clinical and clinical studies. He has discussed some of the pre-clinical protocol with ———— but he has not addressed several issues (GMPs of labs, capability for scale-up, data on drug purity, stability, etc.).

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College of Physicians & Surgeons of Columbia University | *New York, N.Y. 10032*

DEPARTMENT OF PHARMACOLOGY
Telephone (212) 305-8778

630 West 168th Street
Fax (212) 305-8780

March 21, 1994

US FDA
5600 Fishers Lane, Room 14B04
Rockville, MD 20857

Re: Preclinical rat and rabbit studies of RU-486,
in conjunction with Mr. Larry Lader

Dear

I am writing to confirm our telephone discussion of February 14th in which we discussed doses of RU-486 to be utilized in our planned preclinical studies of RU-486. I thank you for your time and interest and greatly appreciate your assistance with this matter. As you may recall, the compound to be utilized for these studies will be synthesized by an FDA-approved contracting laboratory in collaboration with Dr. David Horne of the Chemistry Department at Columbia University. My role will be to guide the planning, conduct and reporting of the preclinical studies in an effort to obtain an IND to study the use of RU-486 as an abortifacient.

Based on our conversation, it is our plan to contract to conduct the following studies, at the dosages listed:

1. A 14-day rat study at doses of 0, 8, 40 and 200 mg/kg/day.

2. A 24-day dog study at doses of 0, 4, 20 and 100 mg/kg/day.

3. A segment II pilot study in rats at 0, 8, 40 and 200 mg/kg/day. The objective of this study is to find a dose which would cause some rat fetuses to be aborted and some retained throughout gestation.

4. A segment II main study in rats at, tentatively, 0, 8, 40 and 200 mg/kg/day.

5. A segment II pilot study in rabbits at 0, 8, 40 and 200 mg/kg/day. The objective of this study is to find a dose which would cause some rabbit fetuses to be aborted and some retained throughout gestation.

6. A segment II main study in rabbits at, tentatively, 0, 8, 40 and 200 mg/kg/day.

If you perceive any basic flaw or deficiency in our preclinical study plan, I would greatly appreciate a response, as the costs associated with the synthesis of the compound and the studies themselves are extraordinarily high. My direct telephone number is 212-305-8368; my fax number is 212-305-8780. Thanks again.

Sincerely,

cc: Mr. Larry Lader
Dr. David Horne

I N T E R O F F I C E M E M O R A N D U M

Date:
From:

Dept:
Tel No:

TO: See Below

Subject: Pre-IND RU-486\Larry Lader

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7 Jul 94
182-39
10:00

The Population Council

Attachment 1

Attendees of the Meeting between the Population Council and the FDA re the NDA for Mifepristone

for the Population Council:
C. Wayne Bardin
George Brown
Margaret Catley-Carlson
Ann Robbins
Irving Spitz
Karon Walker

for

for

The Population Council

Attachment 2

Proposed Agenda for the Meeting between the Population Council and the FDA re the NDA for Mifepristone

1. Why did a year go by with no significant action on the NDA for mifepristone?
2. Overview of the plan for the present submission.
3. Update on the pivotal studies that have been performed in Europe.
4. Review of the clinical protocol.
5. Timeline for the present submission.
6. Selection of a manufacturer.
7. Selection of a distributor.
8. Details of the IND submission.
9. Conclusion

The Population Council

Proposed Agenda for the Meeting between the Population Council and the FDA regarding the NDA Submission for Mifepristone

1. Why did a year go by with no significant action on the NDA for mifepristone?
2. Overview of the plan for the present project.
3. Update on the pivotal studies that have been performed in Europe.
4. Review of the clinical protocol.
5. Timeline for the present submission.
6. Selection of a manufacturer.
7. Selection of a distributor.
8. Details of the IND submission.
9. Conclusion

WHAT HAPPENED IN THE PAST YEAR?

- *21 April 1993* - Roussel announces that the Council can file an NDA
- *16 July 1993* - Council visits FDA
- *Aug 1993* - Negotiations with Roussel slow to the point of no progress
- *Sept 1993* - Roussel makes new demands; Council stops work on IND/NDA
- *16 May 1994* - Roussel assigns patent to the Council for use in U.S.

OVERVIEW OF THE PRESENT PLAN

- Prepare an NDA based on 2 pivotal studies from France and drug supply from Roussel
- Conduct a clinical trial
- Qualify a new site for drug manufacture
- Select a company that will market

DEFINITION

Amenorrhea **is defined as the number of days from the first day of the last menstrual period**

PIVOTAL STUDY I (ROUSSEL)

- Dose Schedule: Day 1: Mifepristone - 600 mg
  Day 3: Misoprostol - 400 μg
- No. of Clinics: 25
- No. of Subjects: 1189

Amenorrhea	≤42	43-49	50-56
No. Subjects	293	724	113
Success Rate (%)	97.3	94.6	94.7

- Comments: The data for 49 days and less formed the basis for the registration of mifepristone and misoprostol in France

of studies we rely on.

PIVOTAL STUDY II (ROUSSEL)

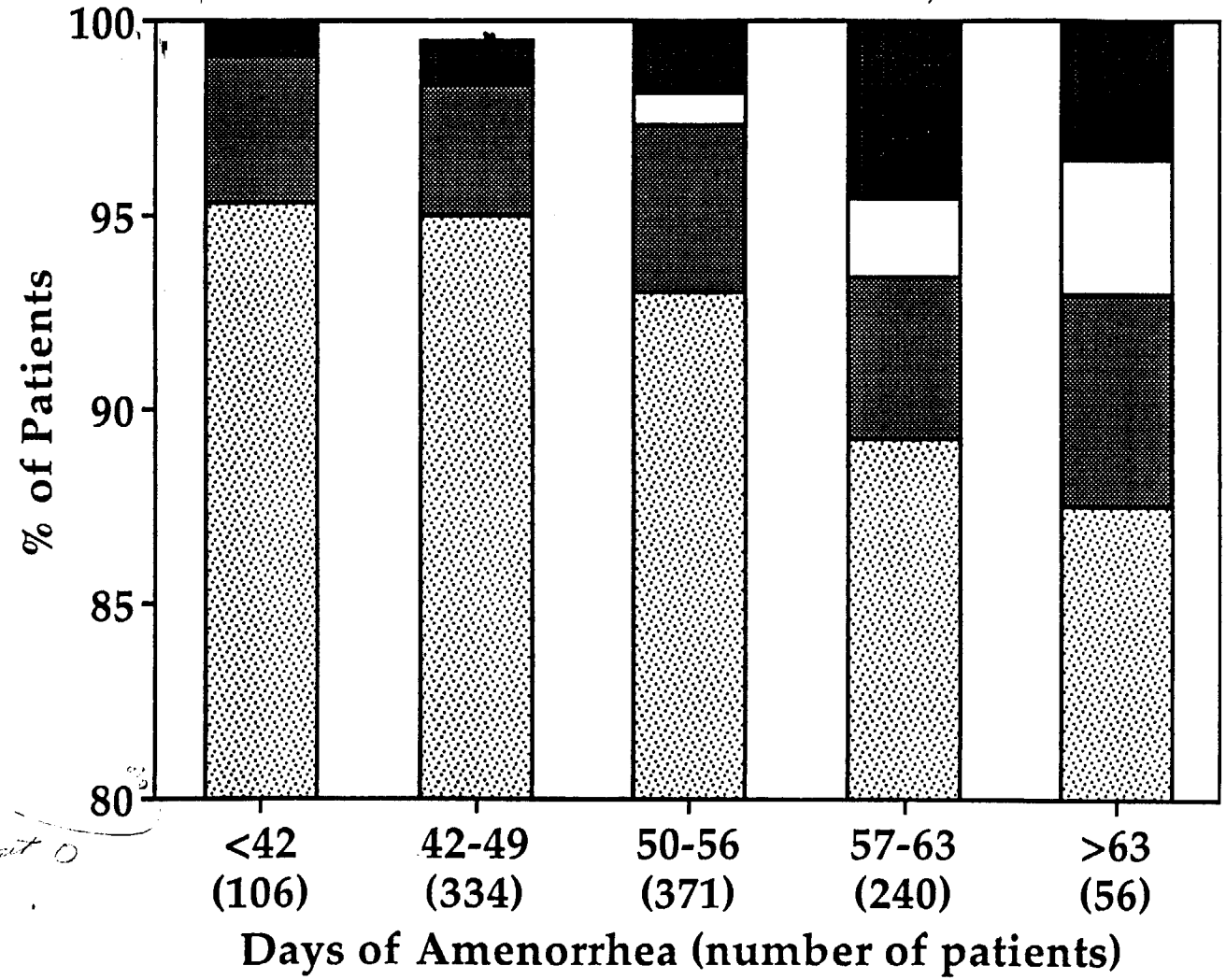
- **Dose Schedule:**
  - **Day 1: Mifepristone - 600 mg**
  - **Day 3: Misoprostol - 400 μg**

- **If abortion failed to occur after 3 hours, subjects were offered an additional dose of misoprostol (200 μg)**

- **No. of Clinics: 11**
- **No. of Subjects: approximately 1,000**
- **Amenorrhea: 49-63 days**

- **Comments: Results are currently being analyzed**

PIVOTAL STUDY II



Roussel, (ongoing study)

AIMS OF THE STUDY

- Back up should pivotal study in France prove unsatisfactory
- Extend the window of use to — days of amenorrhea
- Acceptability and feasibility of the distribution system in the USA

OPTIONS FOR NDA

- Both pivotal studies are acceptable
- Only one pivotal study is acceptable
- Neither pivotal study is acceptable

2 appr. ea 300 women ≤ 49 Days

PROPOSED POPULATION COUNCIL STUDY

- **Dose Schedule:** Day 1: Mifepristone - 600 mg
  Day 3: Misoprostol - 400 μg
- **Study:** Two independent studies each comprising a minimum of 6 clinics
- **Total enrollment:** 2,100 subjects divided into 3 equal groups
- **Group 1:** Amenorrhea less than or equal to 49 days
- **Group 2:** Amenorrhea between 50 and 56 days
- **Group 3:** Amenorrhea between 57 and 63 days
- Each clinic will enroll an additional 15 subjects in a pilot study.

TIME LINE FOR SUBMISSIONS

Ramsel to supply drug.

- Begin audit of pivotal studies
- Amend IND
- Start clinical study - 1st Pat. Ord.
- File NDA in March/April 1995
- Supplemental NDA when clinical study is completed to extend duration of use.

SELECTION OF MANUFACTURER

- Roussel to designate intermediate and the last few steps of synthesis to a proposed manufacturer
- Proposed manufacturer will submit a production plan to the Council
- Submit DMF
- Supply marketer with bulk drug

SELECTION OF "MARKETER"

- Distributer

- Distribute product according to the distribution scheme imposed by Roussel
- File an NDA based on packaging and labeling and cross referencing the Council's NDA

TIME LINE

- Protocol completed
- Complete clinic selection
- IND amendment for Pilot study
- Pilot study (3 clinics) to begin in August
- IND amendment for 2 clinical studies
- Investigator's meeting 3 Oct, 1994
- Trial begins

PROPOSED POPULATION COUNCIL PILOT STUDY

- **Aim of Study:** Assess feasibility of protocol, adequacy of case record forms and investigator's brochure

- **Dose Schedule:** Day 1: Mifepristone - 600 mg
  Day 3: Misoprostol - 400 μg

- **No. of Clinics:** 3

- **Amenorrhea :** up to 63 days

- **No. of Subjects:** 15/clinic; total = 45

Each practitioner's brochure by 1 Aug 94 5 30 day

DETAILED SECTIONS OF THE IND

- Clinical protocol
- Investigator's brochure
- Chemistry and manufacturing
- Teratology and mutagenicity

do not get "officially" ours.
to be filed.

STUDY OUTLINE

VISIT 1 (Day 1)

- History and physical examination
- Determination of duration of amenorrhea
- Urine pregnancy test, vaginal ultrasound
- Determination of blood group, Rh status and hemoglobin
- Ingestion of mifepristone (600 mg)

VISIT 2 (Day 3)

- Interview and clinical examination
- Anti-D globulin (if Rh negative)
- Ingestion of misoprostol (400 μg)
- Observation in study center for 4 hours

VISIT 3 (Day 15)

- Clinical and gynecological examination
- Assessment of treatment outcome (completeness of abortion, bleeding)
- Hemogoblin determination (if necessary)
- Evaluation of acceptability and feasibility of this regimen

/S/

RU 38 486 (RU 486) 19 May 1993
(mifepristone)

Orig Pharm Review 27, 31 Oct 83: The Population Council
IND [redacted] as an early abortifacient.
Rel. IND [redacted]

Includes:
Pharmacology

Acute Tox.: Male Mice and 10 Day M and F Rats (60 mg/kg/day x 10).

30 Day Oral Toxicity Study of RU38486 in the Rat
(Folder 05: 7.2.1. - AL 34 and AL 75)
30 Day Oral Toxicity Study of RU 38486 in Cynomolgus Monkeys (Macaca fascicularis) [Folder 05: 7.2.2. RSL 492/81937]

Preliminary Pharmacokinetic Study of [redacted] RU 38486 in Humans (30 Jul 82)

Studies Received since Orig Review but not reviewed:
Amend 17 May 85:
26 Week Rat

6 mo. Monkey

Present Submission:
Folder 03: Pharmacology, Pharmacology related.
2/13 Reports in French; Some after 1983

Reports 4.1 to 4.9
Reports 5.1.1. to 5.1.3.
Report 5.2.1.

Folder 05: 13 Reports

Reports 7.1.1. to 7.1.7.
Reports 7.2.1. to 7.2.5.
Acute: Oral - rat, mouse, dog. I.P. - rat and mouse
7.2.1. 30-Day oral toxicity study in the rat AL 34 + Additional Report AL 75 (hormone assays) March 1, 1982, Dec. 17, 1981
Pharm Review 27,31 Oct 83
7.2.2. Oral toxicity study in cynomolgus monkey (repeated dosage for 30 days) [redacted] - RSL 492/81937 April 21, 1982
Pharm Review 27,31 Oct 83
7.2.3. RU 38486 - Toxicity to rats in repeated administration by oral gavage over 26 weeks [redacted] - RSL 613/84260 Dec. 27, 1984
7.2.4. 6 month oral toxicity study in cynomolgus monkeys
[redacted] - RSL 604/84146 Jan. 10, 1985
7.2.5. 15-day intravenous toxicology study in rats
86/062/TX Jan 23, 1986

Folder 06: Sub acute Tox 3/4 in French

Reports 7.2.6 to 7.2.9.

7.2.6. Etude de la toxicite chez le singe Macaca fascicularis par voie i.v. pendant 16 jours No1047 TSP 27 fevrier 1986

7.2.7. Etude toxicologie de 30 jours par voie sous cutanee chez le rat — et al 86/083/TX 6 janvier 1986

7.2.8. 30-day subacute repeat dose intramuscular toxicity study in Macaca fascicularis monkey — Study No 1733 — Sept 16, 1986

7.2.9. Etude de la toxicite subaigue par administration intramusculaire repetee pendant 30 jours chez le singe Macaca fascicularis — No 922 — 4 juillet 1985

Folder 07: Mutagenicity, Antigenicity, Ocular, I.M. Irritation etc., and Reproduction, Teratology, Peri-Post Natal Studies including combination with progesterone. 2/23 in French

Reports 7.3.2. to 7.3.13.
Reports 8.1.1.
Reports 8.2.1 to 8.2.8
Reports 8.3.1. and 8.3.2.

Folder 12: Clinical Pharmacology 1/5 in French

Reports 10.1.1 to 10.1.5.

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

Date: 17-Jun-1994 02:00pm DST
From: [redacted]

Dept: HFD-510 PKLN
Tel No: FAX

TO:
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Subject: NOTICE OF FORTHCOMING PRE-NDA MEETING: RU-486

RU-486 (mifepristone) Population Council

NOTCE OF FORTHCOMING MEETING

DATE: JULY 7, 1994
TIME: 10:00 AM - 11:00 AM
PLACE: CR 13B-39

Purpose: The sponsor, in consultation with [redacted] requested this meeting to discuss the Population Council's plans for submitting an NDA for RU-486.

1400
RU 486
Pm

APPEARS THIS WAY
ON ORIGINAL

MIF 008697

RU 486 (RU 38486)

IND — The Population Council
as an early abortifacient
(IND
(RU 486 synthesized by Centre de Recherches Roussel UCLAF (France)

Preclinical Studies:
Antiprogesterone Activity - Roussel UCLAF, Report AL/23 9 Dec 81

General Pharmacology - Roussel UCLAF, Report AM/52, 29 Jul 82

Pharmacological and Toxicological Studies - Roussel UCLAF, Report AK/17
28 Apr 81
Acute Toxicity - Roussel UCLAF, Mice and Rats

30-Day Oral Toxicity Study of RU 38486 in the Rat - Roussel UCLAF, AL 34,
17 Dec 81 0, 8, 40, 200 mg/kg/day

30-Day Oral Toxicity Study of RU 38486 in Cynomolgus Monkeys -
21 Apr 82 0, 4, 20, 100 mg/kg/day

26-Week Oral (Gavage) Toxicity Study of RU 38486 in Charles River Rats -
19 Apr 83 0, 5, 25, 125 mg/kg/day
(not formally reviewed) For Roussel UCLAF

6-Month Oral (intubation) Toxicity Study of RU 38486 in Cynomolgus Monkeys -
10 Jan 85 0, 5, 15, 45 mg/kg/day
(not formally reviewed) For Roussel UCLAF

[Although apparently not officially submitted to the IND (or FDA) we have knowledge that teratology studies have been carried out in 3 species.]

Preliminary Pharmacokinetic Study of ^{3}H RU 38486 in Humans - Roussel UCLAF, 30 July 82

RU 486 (RU 38486)

IND — The Population Council
— as an early abortifacient
(IND —
(RU 486 synthesized by Centre de Recherches Roussel UCLAF (France)

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Preliminary Pharmacokinetic Study of ^{3}H RU 38486 in Humans - Roussel UCLAF, 30 July 82

*** NOTES *** 15 June 1990

Notes for Phone Conference with California FDA 11:30 am

RU 486 (RU 38486)

IND [redacted] the Population Council)
as an early abortifacient
(IND [redacted]
(RU 486 synthesized by Centre de Recherches Roussel UCLAF (France)

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[redacted]

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For Roussel UCLAF (not formally reviewed)

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[redacted]