Elimination

After administration of 3 x 200 mg tritiated mifepristone tablets (i.e., a single oral 600 mg dose), ≈92% of the eliminated radioactivity were found in the feces. Since the bioavailability of mifepristone is ≈70%, the principal route of excretion is biliary. The urinary route is secondary, and renal clearance of mifepristone is minor or negligible compared with its total clearance. The calculated $t_{1/2}$ for mifepristone is 18 hr.

B. Pharmacodynamics (Efficacy)

The efficacy parameter is termination of pregnancy. The sponsor categorizes the response into;

-Success: Complete abortion
-Incomplete: Incomplete abortion
-Failure: Ongoing pregnancy

The following are the results generated from the only clinical study submitted, S/87/486/15, the pivotal pharmacokinetic study.

Table 8

Mifepristone Dose	400 mg (n=20)		600 mg (n=20)	
	# patients	% of n	# patients	% of n
Success	16	80	17	85
Incomplete	0	0	1	5
Failure	4	20	2	10

Although an 85% success rate was seen in these patients, in the clinical trials (data not submitted to DPE II) an ≈95% success rate has been reported.

A search of the biomedical literature yielded the following information concerning the efficacy of various dosage regimens of RU 38 486 in use as an abortifacient in pregnant women of less than 49 days gestational age (Sitruk Ware, R., et al. Contraception 1990; 41: 221-243). It should be noted that the formulation used in this study is unknown and may not proportional to the proposed to-be-marketed formulation outline above.

Table 9

Dosing Regimen	# of Patients	Successful Termination of Pregnancy (%)
400,300,200,100 mg/d in 4 successive days	10	60
50 mg/d × 7d	14	50
100 mg/d × 7d	50	86
450 mg single dose	50	80

From these data it appears that a relatively high single dose of mifepristone is the most effective in the termination of pregnancy.

C. Special Populations

No studies concerning mifepristone pharmacokinetics or pharmacodynamics in renally or hepatically impaired subjects have been submitted.

D. Drug Interactions

Protein Binding

Study number 87/570/CN assessed the displacement of RU 38 486 *in vitro* from plasma proteins by a number of possibly coadministered medications.

The binding of RU 38 486 at a concentration of 5 µM (2.16 mg/mL) in serum is not modified in the presence of therapeutic concentrations of the other following drugs:

Erythromycin:	13.6 µM
Ticlopidine:	5 µM
Disopyramide:	14.7 µM
Cortisol:	0.55 µM
Imipramine:	0.71 µM
Tamoxifen:	0.38 µM
Propranolol:	0.78 µM
Progesterone:	10 nM -100 nM - 800 nM

Metabolism

It has been reported that rat liver CYP3A plays an active role in the "different oxidative pathways of RU 38 486" (Chasserot Golaz S., et al. Biochem Pharmacol 1993; 46: 2100-2103). This was confirmed by increased metabolism in rats pretreated with the CYP3A4 inducer, phenobarbital and decreased metabolism in rats treated with the specific CYP3A4 inhibitor, troleadomycin. It should be noted that an extensive search of the biomedical literature did not yield human metabolic *in vitro* or *in vivo* data for mifepristone and these data are not included in this submission. Since a single dose regimen is indicated for the use of mifepristone as

an abortifacient, the effect of mifepristone on coadministered compounds would be minimal. However, as the proposed package insert indicates ("In addition, drugs known to cause enzyme induction may reduce the efficacy of "Tradename" due to increased metabolism."), compounds that induce enzyme activity (i.e. rifampin) may diminish the efficacy of mifepristone for this indication.

Reviewer Comment:

It is suggested, although not required, that *in vitro* studies be carried out to fully identify the enzymes that catalyze the metabolism of mifepristone.

It should be noted that the above comment was formally communicated to the sponsor on May 20, 1996.

IX. Proposed Labeling

The proposed labeling is included in ATTACHMENT I.

Reviewer Comments:

1. The "Pharmacokinetics/Biopharmaceutics" portion of the CLINICAL PHARMACOLOGY section of the proposed labeling should be formatted to contain subsections entitled; "Absorption", "Distribution", "Metabolism", "Excretion", and "Special Populations", "Hepatically Impaired Patients" and "Renally Impaired Patients".

2. The pharmacokinetic parameters should be reported as mean ± standard deviation.

It should be noted that Comment 1 was formally communicated to the sponsor on May 20, 1996.

NDA 20-687

APPENDIX I
***In Vitro* Studies**

86/274/CN
87/591/CN
88/739/CN
87/570/CN

Study Number: 86/274/CN

Study Title: *In Vitro* Study of the Blood Binding of RU 38 486 in Man

Study Dates: Not specified (Report dated September, 1986)

Study Director: [redacted]

Study Design: *In vitro* study by equilibrium dialysis

Study Population: Study performed on serum from healthy human volunteers

Study Drug: Tritiated RU 486 in pooled serum from healthy volunteers at a dosage of 1.87 Tbq/m mole (50.6Ci/m mole)

Statistical Methodology Employed:
The serum binding percentages of ^{3}H-RU 38 486 were compared by a Mann-Whitney test.

Results:
The characteristics of the blood from healthy volunteers used to study the blood binding of RU 38 486 are outlined in Table 10.

Table 10

Hematocrit (%)	45
HSA (μM)	694
α_1 acid glycoprotein (μM)	11.2
Bilirubin (μM)	7
Free fatty acids	
Linoleic Acid (μM)	67
Myristic Acid (μM)	20
Oleic Acid (μM)	113
Palmitic Acid (μM)	113
Palmitoleic Acid (μM)	20
Stearic Acid (μM)	41

The binding parameters for various serum proteins and erythrocytes is included in Table 11.

Table 11

Proteins	n (# binding sites)	Kα (M^{-1})	nKα (M^{-1})
HSA			32000 ± 438
α_1 acid glycoprotein	0.9 ± 0.02	$8\times10^6 \pm 0.5\times10^6$	$7.2\times10^6 \pm 0.5\times10^6$
VLDL			$33\times10^6 \pm 2.5\times10^6$
LDL			$3.5\times10^6 \pm 0.09\times10^6$
HDL			$1.6\times10^6 \pm 0.08\times10^6$
γ globulin			$0.109\times10^6 \pm 0.007\times10^6$
erythrocytes			NK = 0.4 ± 0.008

The percent of RU 38 486 bound to serum at concentration of 0.01 to 10 μg/ml are outlined in Table 12.

Table 12

Concentrations of RU 38 486		Percent Bound
mg/L	μM	
10	23.06	98.25 ± 0.32
5	11.53	98.18 ± 0.44
4	9.224	98.30 ± 0.38
3	6.918	97.93 ± 0.50
2	4.612	97.98 ± 0.27
1.5	3.459	97.92 ± 0.47
1	2.306	98.01 ± 0.34
0.75	1.7295	97.66 ± 0.61
0.5	1.153	97.86 ± 0.42
0.25	0.5765	98.69 ± 0.15
0.1	0.2306	98.38 ± 0.25
0.01	0.02306	98.22 ± 0.17
Mean ± SEM		98.115 ± 0.26

The distribution (%) of the binding of RU 38 486 between various serum proteins are as follows'

Table 13.

	μM	%
α_1 acid glycoprotein	18.4	68.5
HSA	600	9.9
VLDL	0.0792	1.3
LDL	1.52	2.7
HDL	14.8	12.2
γ globulin	87.5	4.9
Bound RU 38 486		99.5
Unbound RU 38 486		0.5

Graphs of concentration of bound versus unbound RU 38 486 indicate that this compound is saturably bound to AAG but not to HSA, VLDL, LDL, HDL, γ-GB or erythrocytes (raw data not submitted, therefore not reanalyzed and not presented here).

Sponsor's Conclusions:
In serum, RU 38 486 was 98% bound at concentrations ranging from 0.023 to 23μM (0.01 to 10mg/l). In blood, the binding of RU 38 486 to erythrocytes was negligible.

Binding to α_1-acid glycoprotein by RU 38 486 is by a saturable process. This binding is characterized by a very high affinity ($Ka=8x10^6\ M^{-1}$).

Binding to the other plasma proteins is non-saturable. Human serum albumin accounts for 9.9% of the serum binding of RU 38 486, lipoproteins 16.2% and human gamma-globulins 4.9%.

AAG is the only protein showing saturable binding of RU 38 486 with a single high affinity binding site. Since there is only a single binding site, the binding capacity of AAG is at most equal to its molar concentration. *In vitro*, when the concentration of RU 38 486 exceeds that of AAG, the excess of RU 38 486 may bind to the other serum proteins, giving a constant percentage binding.

Reviewer Comment:
I concur with the sponsor's conclusions.

It should be noted that the amount of AAG used in these *in vitro* studies are an order of magnitude lower than those measured in normal pregnant females (0.036 g/L versus ≈0.6 g/L, results from study 87/592/CN).

Study Number: 87/591/CN

Study Title: *In Vitro* Study of Binding of RU 38 486 and RU 42 633 to Human α_1-Acid Glycoprotein and Albumin

Study Dates: Not specified (report dated September, 1987)

Study Director: [redacted]

Study Design: *In vitro* study by equilibrium dialysis

Study Population: Study was performed *in vitro* on human serum

Study Drug: Tritiated RU 38 486 (specific activity 50.6 Ci/m mole) in buffered protein solutions at 10 or 20 µM, RU 42 633 (specific activity 49.2 Ci/m mole) in buffered protein solution at 10 or 20 µM

Preliminary Evaluation Parameters:

1. Binding to α_1 glycoprotein at physiological concentrations
2. Binding RU 42 633 for α_1 glycoprotein
3. The role of albumin in binding excess RU 38 486 or RU 42 633 *in vitro* when α_1 glycoprotein is saturated.

Results:

The percentage binding was the same for both compounds. In the case of AAG, binding percentage decreased from 86-87% to 71-75% when the concentration of compound increased from 10 to 20 µM .

RU 38 486 and RU 42 633 have the same percentage binding to HSA and AAG. Binding to AAG is saturable and the two compounds compete for the binding site. Saturation is achieved when the sum of their molar concentrations is equal to or greater than that of AAG. Binding to HSA is not saturable and *in vitro* the excess compound which cannot bind to saturated AAG binds to HSA. For HSA and HSA + AAG, binding was always the same, 93-94% and 97-99% respectively.

Study Number: 88/739/CN

Study Title: *In Vitro* Study of the Blood Binding of RU 42 633 in Man

Study Dates: Not specified (report dated February, 1988)

Study Director: [redacted]

Study Design: *In vitro* study by equilibrium dialysis

Study Population: Study performed *in vitro* on serum of human volunteers

Study Drug: Tritiated RU 42 633 in pooled serum

Preliminary Evaluation Parameters:
Measurement of percentage of ^{3}H RU 42 633 binding to serum proteins and erythrocytes to determine the binding constants of the different proteins.

Statistical Methodology Employed:
Mann-Whitney test

Results:
In serum RU 42 633 was 98% bound at concentrations ranging from 0.023 to 23.8 μM. In blood, binding to erythrocytes was negligible.

Among the serum proteins, AAG is the only protein which demonstrates specific saturable binding of RU 42 633 with a high affinity at a single binding site.

Simulation shows that at non-saturating concentrations of RU 42 633 it is the only principal binding protein in serum.

When the concentrations of RU 42 633 are such that AAG is saturated, the excess RU 42 633 binds to the other serum proteins. For this reason the percentage binding in serum remains constant, even at high concentrations of RU 42 633 (up to 23.8 μM).

Study Number: 87/570/CN

Study Title: Study of Plasma Drug Interactions with RU 38 486

Study Dates: Not specified (report dated March, 1987)

Study Director: [redacted]

Study Design: *In vitro*, binding of RU 38 486 with human plasma

Study Population: Study performed *in vitro* on human sera

Study Drug: RU 38 486

Preliminary Evaluation Parameters:
To determine whether the study drug is bound at AAG site, and whether at therapeutic concentrations, competition phenomena can be observed with study drug and other medications, including Erythromycin, Disopyramide, Imipramine, Propranolol, Ticlopidine, Cortisol, Tamoxifen, Progesterone, and the metabolites of RU 38 486 (RU 42 688, RU 42 633 and RU 42 848).

Statistical Methodology Employed:
Percentages of binding of study drug and other drugs compared using Mann-Whitney test.

Results:
The binding of RU 38 486 at the therapeutic concentration 5 µM (2.16 mg/mL) in serum is not modified in the presence of therapeutic concentrations of the other following drugs:

Erythromycin:	13.6 µM	Ticlopidine:	5 µM
Disopyramide:	14.7 µM	Cortisol:	0.55 µM
Imipramine:	0.71 µM	Tamoxifen:	0.38 µM
Propranolol:	0.78 µM	Progesterone:	10 nM -100 nM - 800 nM

Under the same experimental conditions, the Mann and Whitney test shows a significant decrease in the binding of RU 38 486 by its three metabolites: RU 42 698 1.03 µM, RU 42 633 3.88 mm, and RU 42 848 1.86 mm.

The binding of RU 38 486 at therapeutic concentrations in the presence of isolated AAG at physiological concentrations is not modified by the therapeutic concentrations of the other drugs. There is a significant decrease in RU 38 486 when it is in the presence of its three metabolites.

The binding of RU 38 486 at therapeutic concentrations in the presence of isolated AAG 18.4 µM (0.9 g/L) is modified significantly by molar concentrations of drugs such that the drug/ RU 38 486 molar ratio = 100.

At therapeutic concentrations of study drug, there is no possible plasma AAG saturation.

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APPENDIX II
Pilot Pharmacokinetic Studies

87/593/CN
87/601/CN
87/592/CN
86/257/CN

Study Number: 87/593/CN

Title: Study of the Plasma Pharmacokinetic Parameters of RU 38 486 Administered in a Single Oral Dose of 600 mg to Women

Study Dates: February - April 1987

Study Director:

Study Design: Randomized open-label cross-over study

Study Population: Ten healthy female volunteers, aged 20 to 32 years (26.5 mean)

Study Drug: RU 38 486 administered in a single oral dose (3 × 200 mg tablets)

Assay Validation:
RU 38 486 and RU 42 633 were analyzed in plasma using an method. The sensitivity limit of the assay was set at and samples with were considered to be zero.

Quality control samples were included 10 replicates at each of three concentrations were analyzed.

Analyte	Concentration	Coefficient of variation (n=10)
RU 38 486	0.082 mg/L	7.1%
	0.816 mg/L	2.5%
	1.326 mg/L	2.7%
RU 42 633	0.083 mg/L	6.8%
	0.832 mg/L	3.0%
	1.352 mg/L	2.1%

Statistical Methodology Employed:
2-way analysis of variance (product, subject). Calculation of the coefficient of correlation (r) and the equations of the regression lines between the pharmacokinetic parameters and α_1-acid glycoprotein (AAG).

Results:
The mean plasma AAG levels in the subjects included in this study was 0.647 ± 0.058 g/L.

The pharmacokinetic parameters after administration of 600 mg of mifepristone observed in this study are included in Table 14.

Table 14.

Parameter	RU 38 486 (parent)	RU 42 433 (metabolite)
Cmax (mg/L)	1.98 ± 0.31	1.66 ± 0.19
Tmax (h)	1.35 ± 0.31	4.30 ± 0.70
AUC (mg×h/L)	71 ± 10	98 ± 13
MRT (h)	47.1 ± 3.4	51.2 ± 3.7
t½ (h)	17.5 ± 1.0	22.0 ± 2.3

The mean plasma concentration versus time profiles of RU 38 486 and RU 42 633 for 24 hours after the dose is represented in Figure 8. This figure allows for closer inspection of the absorption and distribution phases of mifepristone and metabolite. The sponsor characterizes the plasma concentration versus time profile of RU 38 486 by a rapid absorption phase followed by a distribution phase and a bi-exponential elimination phase, slow initially (12 h to 72 h post-dose) and then a rapid terminal phase (>120 h post-dose). Cmax and AUC positively correlated with AAG (see Table 15), thus showing that the volume of distribution and clearance of RU 38 486 and RU 42 633 increase when AAG is low or when the bonding capacity of AAG is exceeded.

Figure 15

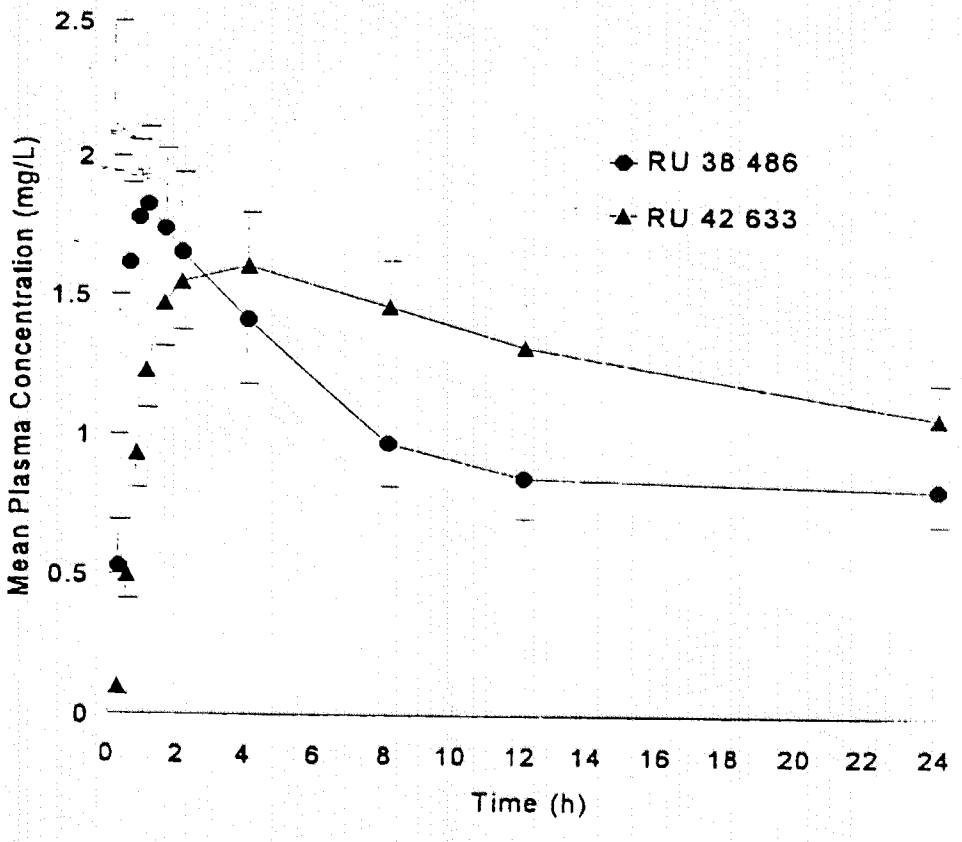


Table 16. Correlation Between the Pharmacokinetic Parameters of Mifepristone and AAG

	RU 38 486		RU 42 633	
	r	p	r	p
Cmax (mg/L)	0.925	<0.001	0.830	0.01≥p>0.001
AUC (mg×h/L)	0.784	0.01≥p>0.001	0.701	0.05≥0.01
t½ (h)	0.481	N.S.	0.380	N.S.

Sponsor's Conclusions:

1. Cmax and AUC were correlated with plasma α_1-acid glycoprotein (AAG), thus showing that the volume of distribution and the clearance of RU 38 486 and RU 42 633 increase when AAG is low or when its binding capacity is exceeded.

2. The time course of the plasma concentrations of RU 38 486 have a particular profile: after a rapid absorption phase followed by a distribution phase (1-8 hr post dose), elimination is at first slow (the concentration between 12 and 72 h decreases by about a half from 0.84 to 0.43 mg/L), but then becomes more rapid, resulting in a t½ of 17.5 h calculated from the later concentrations (120 h or longer).

3. Despite the significantly different pharmacokinetic parameters (except for Cmax), the concentrations of RU 42 633 have the same profile (*I assume the same as RU 38 486*).

4. Clinically, the particular pharmacokinetics of RU 38 486 mean that, after administration of 600 mg on an empty stomach, greater extravascular diffusion and concentrations which remain high for 3 days may be obtained.

Reviewer Comments:

1. The portion of the curve (1-8 hr post-dose) the sponsor characterizes as the distribution phase, may have a significant elimination component of the unbound RU 38 486 and RU 42 633 that has been proven to saturably bind to AAG.

2. The elimination of RU 38 486 and RU 42 633 may be similar, but the plasma concentration versus time profiles of the parent and metabolite are not the same as the sponsor concludes.

Study Number: 87/601/CN

Title: Plasma Kinetics and Excretion of Radioactivity in Women after Oral Administration of 600 mg of RU 38 486

Study Dates: June - August 1987

Study Director: [redacted]

Study Design: Open-label

Study Population: Four healthy, non-pregnant, female volunteers aged 24-33 years

Study Drug: RU 38 486 labeled with tritium in position 6 and 7 (18.4µCi/ tablet) administered in a single dose (3 x 200 mg tablets)

Radiometric Assay:
The limit of detection of radioactivity was equivalent to [redacted] in the plasma.

Results:
Biological stability was tested by measuring the amount of tritiated water present on days 5 and 10 after dosing. The results of this analysis are presented in Table 17. It is apparent that on average <0.5% of the radioactivity is lost to instability per day.

Table 17.

Collection Time	% of Dose (mean ± SEM)
96-120 h (DAY 5)	0.47 ± 0.05
216-240 h (DAY 10)	0.45 ± 0.04

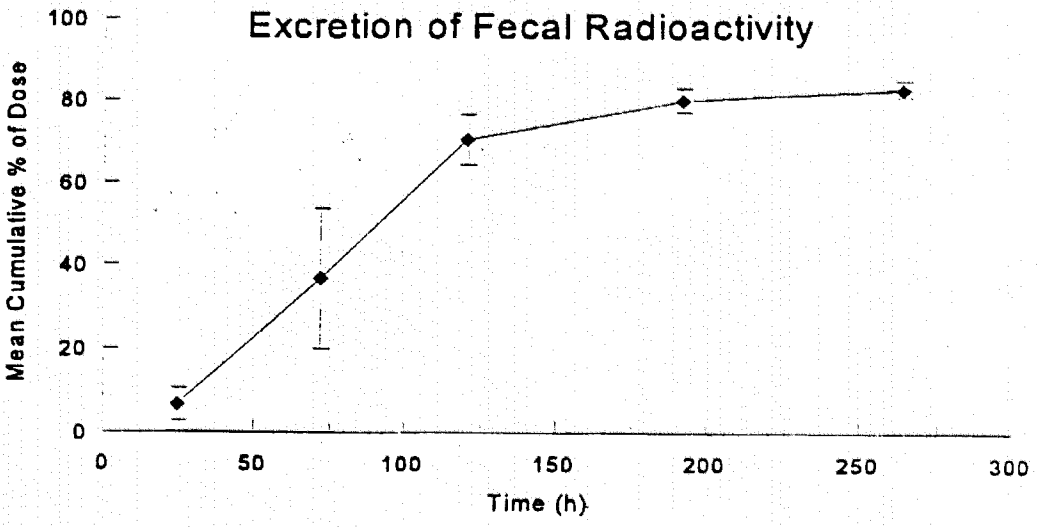
The excretion of mifepristone is primarily by the fecal route while the kidneys play a relatively minor role. The biological fate of the dose up to 11 days post-dose is outlined in Table 18.

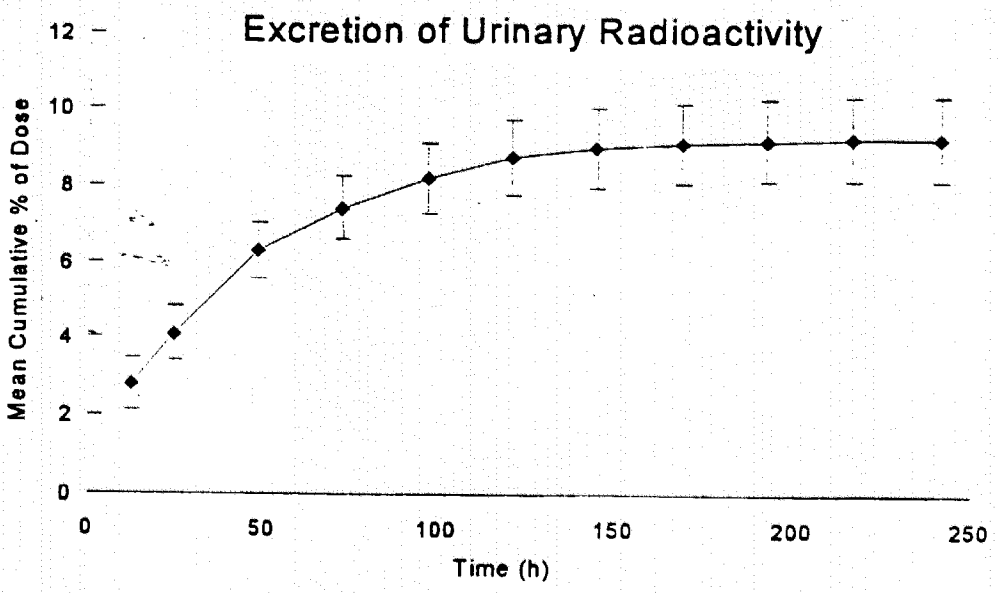
Table 18.

Biological Material	Collection Time (h)	% of Dose (mean ± SEM)
Urine	240	9.2 ± 1.1
Feces	264	83.1 ± 1.9
Total		92.3 ± 0.8

% of dose = radioactivity which includes parent + metabolites

Figure 9





It should be noted that at 10 days post-dose, no further renal excretion was seen. However, a small amount of radioactivity was seen in the feces on Day 11, indicating that fecal mifepristone excretion was not completed 11 days post-dose.

Sponsor's Conclusions:

1. The biological stability of the radiolabeling of mifepristone was good, less than <0.5% degradation was observed per day.

2. Excretion was satisfactory. At the end of the collection there was no more radioactivity detectable in the urine, but a small amount remained in the feces (maximum 0.83% at 264 h). Of the 92.3% of the dose eliminated, 10% were eliminated in the urine and 90% in the feces.

3. Despite the high administered dose, the Cmax was 5.8 mg/L or 13.5 μM in RU 38 486 equivalent, and the plasma profile of radioactivity was similar to that observed elsewhere for RU 38 486 and its metabolites after a high dose.

Reviewer Comments:

I concur with the sponsor's conclusions from study 87/601/CN.

Study Number: 87/592/CN

Study Title: Absolute Bioavailability Study of RU 38 486 Administered in a Single 20 mg Dose to Women

Study Dates: November, 1986- January, 1987

Study Director: [redacted]

Study Design: Open, randomized, in crossover Latin square study

Study Population: Ten healthy female, non-pregnant, volunteers, 20- 32 years of age (26.5 mean)

Study Drug: RU 38 486 administered in a single 20 mg dose either by IV or orally in 120 ml of water (20 mg in 100 ml of 0.9% sodium chloride administered over 1 hour)

Assay Validation:

RU 38 486 and RU 42 633 were analyzed in plasma by an [redacted] method. AAG was analyzed by a [redacted] method.

AAG

Calibration was done with a range of standard sera from [redacted] g AAG/L. All assays were run in duplicate with standards applied to each plate used.

RU 38 486 and RU 42 633

The limit of quantification was set at [redacted] and concentration below the limit of quantification were considered zero.

Quality control samples were included every 18 samples. Ten replicates at each of three concentrations were analyzed.

Analyte	Concentration	Coefficient of variation (n=10)
RU 38 486	0.075 mg/L	3.3%
	0.300 mg/L	4.8%
	1.600 mg/L	2.6%
RU 42 633	0.076 mg/L	5.3%
	0.305 mg/L	3.7%
	1.626 mg/L	2.8%

Statistical Methodology Employed:
3-factoral (treatment, subject, period) and 2-factoral (product, subject) analysis of variance.
Calculation of the coefficient of correlation between AAG and the pharmacokinetic parameters.

Results:
The pharmacokinetic parameters resulting from the intravenous and oral dosing of 20 mg of mifepristone are included in Table 19 and the mean plasma levels are represented in Figure 10.

Table 19

	Intravenous		Oral	
AAG (g/L)	0.635 ± 0.031		0.642 ± 0.044	
PK Parameter	RU 38 486	RU 42 633	RU 38 486	RU 42 633
Cmax (mg/L)	1.49 ± 0.12	0.317 ± 0.029	0.957 ± 0.091	0.554 ± 0.022
Tmax (h)	1.00 ± 0	9.1 ± 2.0	0.625 ± 0.067	0.98 ± 0.13
AUC (mg×h/L)	11.2 ± 1.2	12.3 ± 1.3	6.87 ± 0.86	12.1 ± 1.3
MRT (h)	15.6 ± 1.3	26.2 ± 1.9	14.4 ± 1.2	20.7 ± 1.6
t½ (h)	16.7 ± 1.6	19.3 ± 2.3	14.8 ± 1.0	16.2 ± 1.3
Cl (L/h)	2.01 ± 0.23	-	-	-
Vd (L)	47.0 ± 5.6	-	-	-
F	-	-	0.69 ± 0.13	1.09 ± 0.16

Figure 10. Mean ± SEM Plasma RU 38 486 Concentration (Bioavailability)

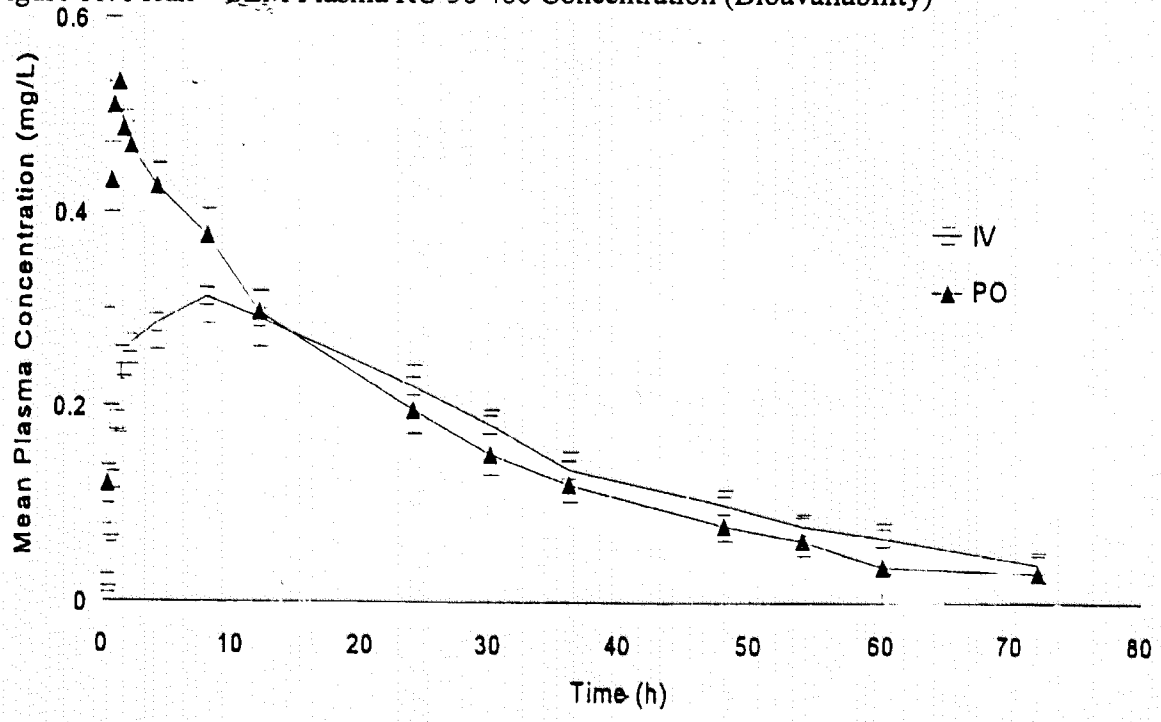
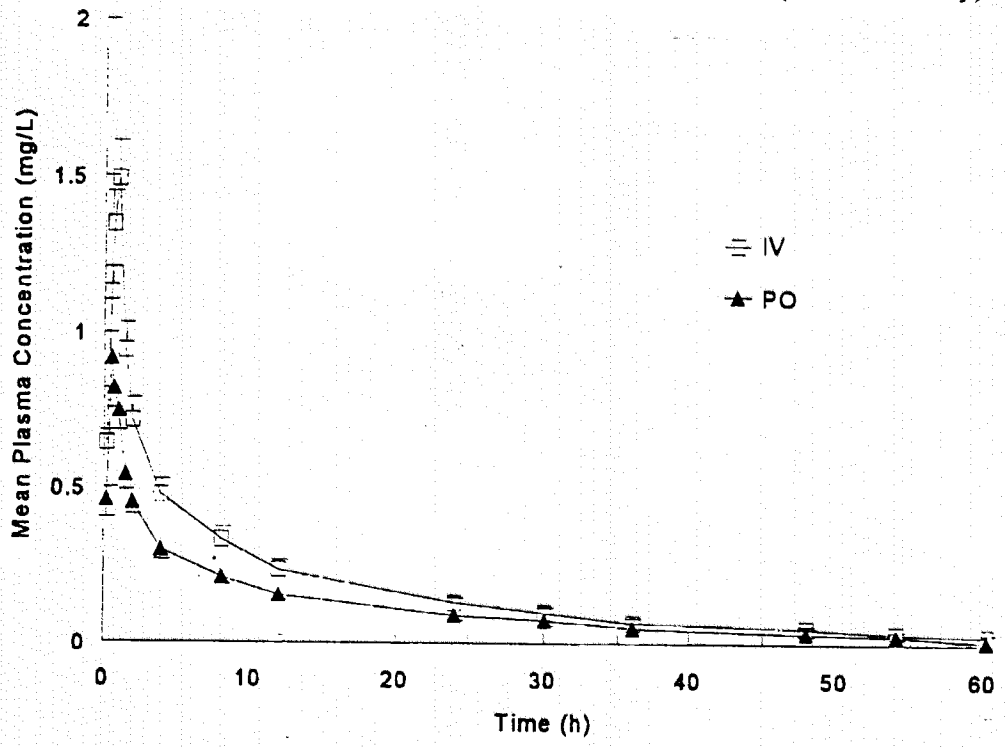


Figure 11 Mean ± SEM Plasma RU 42 633 Concentration (Bioavailability)



Sponsor's Conclusions:

1. Administered in a dose of 20 mg, RU 38 486 displayed a constant volume of distribution and clearance over time.

2. The plasma kinetics of RU 38 486 were dependent on the concentration of AAG, and Vd and Cl in particular was lower in patients with lower serum concentrations of AAG increased (data not shown in review). In three subjects AAG, and consequently Vd and Cl, varied between the two treatments. F was calculated from the ratio of the areas and from the clearance calculated after PO treatment as a function of AAG. The mean results obtained by both methods of calculation were the same, the individual variations offsetting one another.

3. The absolute bioavailability of oral RU 38 486 was good: absorption was very rapid and total, 69% reaching the organism intact after a slight first pass effect.

Reviewer Comments:

I concur with the sponsor's conclusions from study 87/592/CN. However, it should be pointed out that the proposed dose of 600 mg mifepristone is >10 times that given in this study.