

**Study Number:** 86/257/CN

**Study Title:** Plasma Kinetics of RU 38 486 and Some of its Metabolites in Female Subjects after a Single Oral Administration of 50, 150 or 450 mg of RU 38 486. Linearity Study.

**Study Dates:** Not specified (report dated September, 1986)

**Study Director:** [REDACTED]

**Study Design:** Randomized, uncontrolled, open, cross-over (linearity) study

**Study Population:** Twelve non-pregnant healthy female volunteers 20 to 40 years of age (28.3 mean)

**Study Drug:** RU 38 486 administered to each subject in 3 doses (50 1×50mg, 150 3×50mg, or 450mg 9×50 mg)

**Assay Validation:**

RU 38 486 and RU 42 633 were analyzed by an [REDACTED] method. Quality control samples of spiked plasma so as to contain 50, 100 and 200 ng/ml of RU 38 486 and each metabolite. The data from 10 replicates of each concentration of each metabolite is included below.

Analyte	% of Concentration Recovered ± SEM
RU 38 486	98 ± 0.2%
RU 42 698	87 ± 0.8%
RU 42 633	70 ± 1.7%
RU 42 848	47 ± 0.6%

These yields did not effect the measured plasma concentrations, since the calibration curves were established from spiked plasma and accounted for the extraction yield.

**Statistical Methodology Employed:**

Pharmacokinetic parameters were subjected to a 3-way analysis of variance with the mean, variance and standard error of the mean of the parameters being calculated for each compound.

**Results:**

The mean ± SEM of the principle pharmacokinetic parameters generated from doses of 50, 150 and 450 mg of mifepristone are included in Table 20.

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Table 20.

Parameter	Dose (mg)	RU 38 486	RU 42 633	RU 42 698	RU 42 848
Tmax (h)	50	1.13 ± 0.17	2.25 ± 0.33	2.58 ± 0.31	23.7 ± 5.1
	150	0.90 ± 0.15	4.08 ± 1.84	2.58 ± 0.33	11.3 ± 1.8
	450	1.00 ± 0.14	3.79 ± 0.94	3.21 ± 0.55	14.7 ± 3.5
Cmax (mg/L)	50	1.22 ± 0.14	0.73 ± 0.07	0.223 ± 0.023	0.261 ± 0.020
	150	1.75 ± 0.23	1.28 ± 0.12	0.353 ± 0.035	0.569 ± 0.058
	450	2.05 ± 0.16	1.61 ± 0.13	0.463 ± 0.044	0.737 ± 0.077
AUC (mg×h/L)	50	17.4 ± 1.8	23.6 ± 2.1	5.8 ± 0.7	17.2 ± 1.6
	150	28.8 ± 3.9	39.5 ± 4.1	9.6 ± 1.5	31.0 ± 4.1
	450	63.6 ± 5.9	74.3 ± 6.0	21.7 ± 2.1	54.8 ± 5.7
MRT (h)	50	24.6 ± 2.2	30.3 ± 2.1	25.2 ± 2.5	43.5 ± 2.5
	150	28.0 ± 2.0	30.2 ± 1.8	27.5 ± 2.1	41.7 ± 2.3
	450	41.4 ± 1.5	41.8 ± 1.5	42.8 ± 1.8	51.3 ± 1.6
t½	50	20.2 ± 1.5	20.7 ± 1.3	21.6 ± 1.4	25.0 ± 2.2
	150	20.1 ± 1.4	24.1 ± 1.8	25.5 ± 2.0	35.3 ± 5.9
	450	32.4 ± 3.3	40.4 ± 3.4	41.9 ± 3.8	60.2 ± 10.0

The kinetics of RU 38 486 are not linear. Cmax and AUC were not directly proportional to dose. MRT and t½ were longer at the highest dose (450 mg). When the dose of RU 38 486 was multiplied by 9, the mean peak concentration was multiplied by 1.7 and AUC by 3.7. The three metabolites analyzed in this study have non-linear kinetic behavior similar to that of RU 38 486. The non-linearity of RU 38 486 kinetics is the result of saturable binding to  $\alpha_1$ -acid glycoprotein.

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Figure 12. Mean Plasma RU 38 486 Concentration versus Time, Dose Ranging

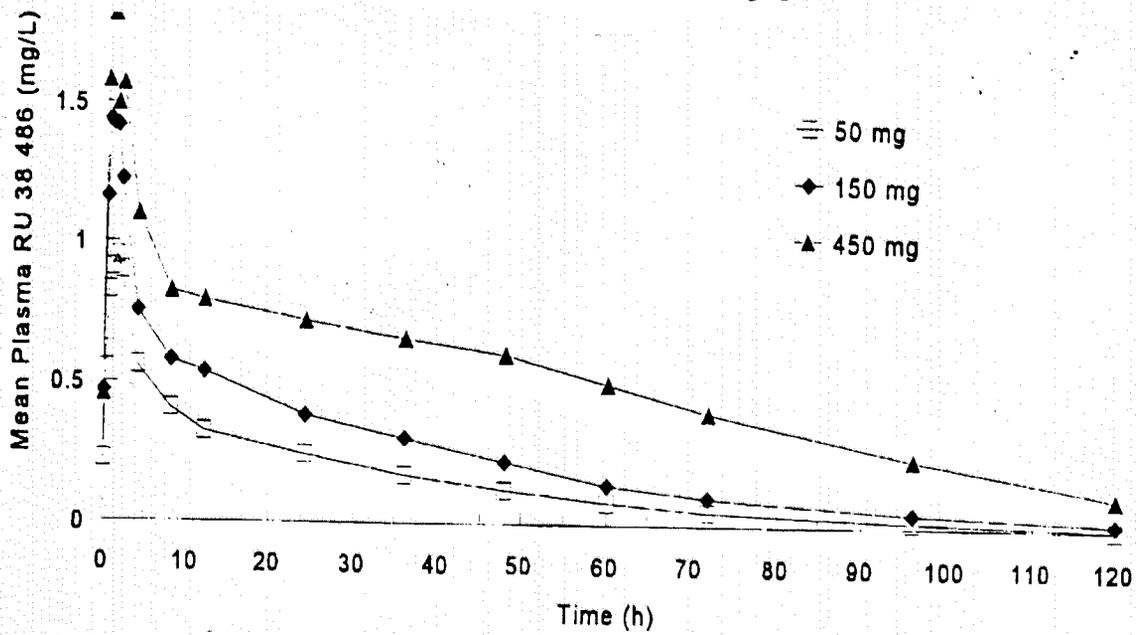
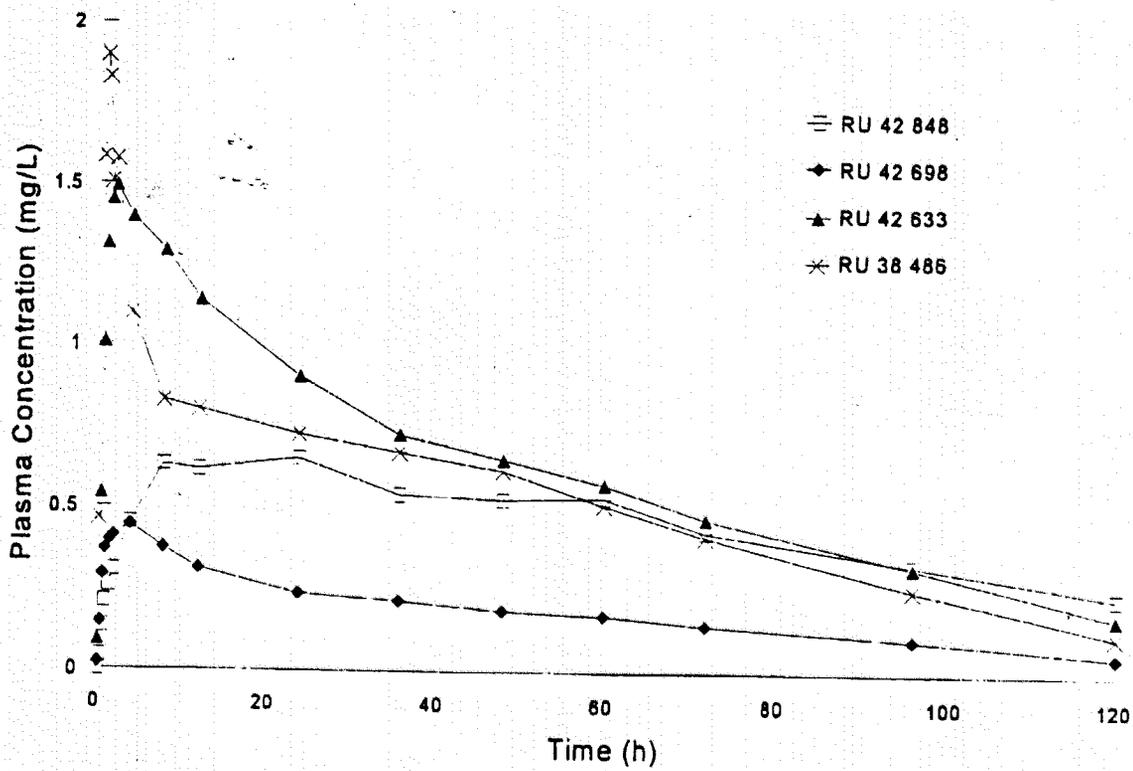


Figure 13. Mean Plasma Concentration of RU 38 486 and Metabolites After a Dose of 450 mg of Mifepristone



**Sponsor's Conclusions:**

1. The plasma concentration of RU 38 486 and 3 of its metabolites, RU 42 633, RU 42 698 and RU 42 848, after administration of 3 single doses of RU 38 486 (50, 150 and 450 mg) to 12 young women in a randomized crossover study showed that the pharmacokinetics of RU 38 486 and its metabolites are NOT linear.
2. When the dose of RU 38 486 was increased nine fold, the mean peak concentration was increased only by a factor of 1.7 and AUC by 3.7. Its  $t_{1/2}$ , which was 20 h after the 50 and 150 mg doses, increased to 32 h after the 450 mg dose. Its absorption and metabolism did not seem to be modified by the dose and the cause of the non-linearity of its PK may be seen in the saturable nature of its binding to plasma protein.
3. The metabolites have a similar kinetic behavior to that of RU 38 486.
4. In practical terms, the specific pharmacokinetics of RU 38 486, after a high single dose (of the order of 450 mg or more), should yield greater extravascular diffusion (the volume of distribution is increased by the dose) and concentrations which decrease very slowly (clearance being increased less than the volume of distribution at high doses).

**Reviewer Comments:**

1. The kinetics of RU 38 486 are not linear over a range of 50 to 450 mg and data from study 87/486/15 indicate that doses of 450 and 600 mg are also not linear. This non-linearity is due to the saturable binding of RU 38 486 to AAG. This binding is complicated by the fact that at least one metabolite, RU 42 633, also binds to AAG and competes with RU 38 486 for the AAG binding site. It also appears from study 87/486/15, that doses of 450 and 600 mg of mifepristone incur levels of active compound that are up to 85% effective and clinical reports indicate that a dose of 600 mg is up to 95% effective as an abortifacient.
2. The proposed to-be-marketed dosing regimen is a single oral dose of 600 mg of mifepristone. Therefore, the lack of dose proportionality seen in this study is of little clinical consequence.

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APPENDIX III  
*PIVOTAL PHARMACOKINETIC/PHARMACODYNAMIC STUDY*

S87/486/15

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**Study Number:** S/87/486/15

**Study Title:** Changes in the Plasma Concentrations of RU 38 486 and RU 42 633 in Women During Pregnancy Termination

**Study Dates:** 12/2/88 - 3/20/89

**Study Director:**

**Study Design:** Open, randomized

**Study Population:**

Forty-one (40 completed) Healthy human female volunteers aged between 18 and 45 years wishing to undergo a termination of pregnancy of less than 49 days.

**Study Drug:** 200 mg tablet of RU 38 486, batch  21 236-50

**Assay Validation:**

RU 38 486 and RU 42 633 were analyzed by an  method.

**Sensitivity:**  for a 0.3 ml sample

**Specificity:** The blank plasma exhibited no  at the retention times of mifepristone, RU 42 633, and RU 39 813 (internal standard), and the other potential metabolites, RU 42 698 and RU 42 848, have substantially shorter retention times than the analytes of interest.

**Precision (coefficients of variation limits):**

RU 38 486:

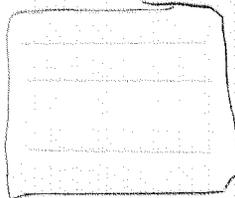
First Batch

Second Batch

RU 42 633:

First Batch

Second Batch



**Statistical Methodology Employed:**

- ▶ One-way analysis of variance: dose and/or physiological status combined.
- ▶ Two-way analysis of variance: compounds assayed and subjects.
- ▶ Test for a correlation between the pharmacokinetic parameters and the mean concentration of AAG for RU 38 486 and RU 42 633.

**Results:**

The mean of the pharmacokinetic parameters observed after single oral doses of mifepristone are presented in Table 21 ( $\pm$  standard deviation) and illustrated in Figure 14 ( $\pm$  SEM);

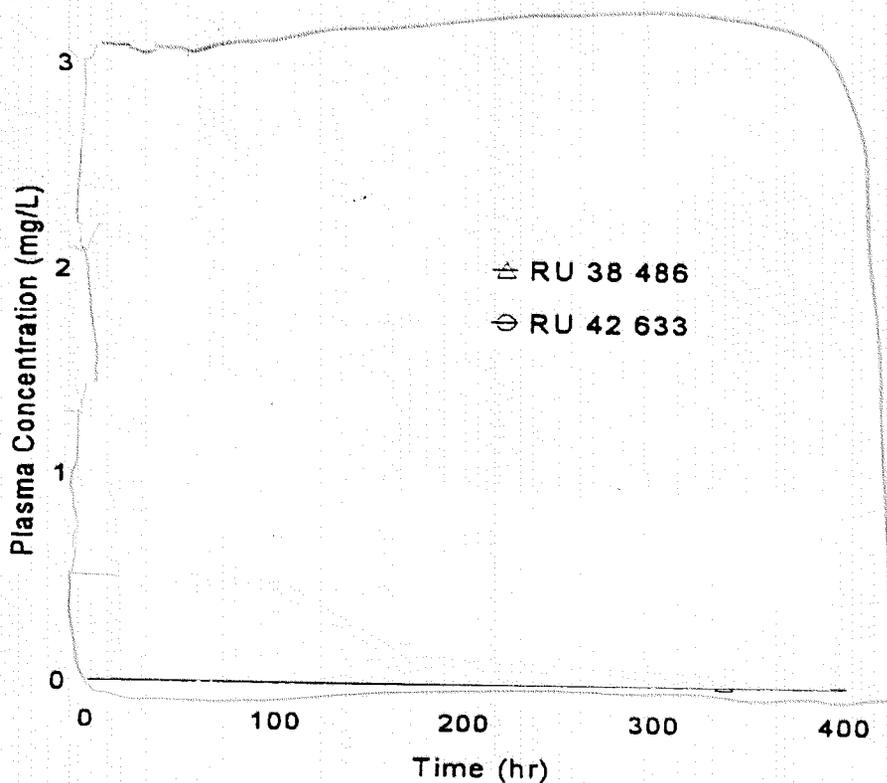
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Table 21

	400 mg (n=20)		600 mg (n=20)	
	RU 38 486	RU 42 633	RU 38 486	RU 42 633
Tmax (h)	1.25 ± 0.54	3.2 ± 4.9	1.45 ± 0.59	3.25 ± 1.8
Cmax (mg/L)	2.70 ± 0.98	2.07 ± 0.60	2.56 ± 0.78	2.16 ± 0.40
AUC (mg*h/L)	78.7 ± 34.9	96.6 ± 38.9	106 ± 68	130 ± 74
MRT (h)	39.5 ± 11.5	43.6 ± 13.0	50.5 ± 21.2	52.4 ± 25.4

These data indicate the lack of dose proportionality in Cmax values between 400 and 600 mg doses of mifepristone, although AUC appears to be dose proportional.

Figure 14



It is apparent from the graphs below (Figures 15, 16 and 17) that the pharmacokinetics of mifepristone is correlated with plasma AAG levels. This is confirmed by the protein binding studies which indicated mifepristone binding to AAG in a saturable manner.

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Figure 15. Correlation Between Plasma AAG and Mifepristone Cmax (single 600 mg dose)

Regression Output	
Intercept	0.115
Std Err of Y Est	0.636
R <sup>2</sup>	0.402
Slope	2.399
Std Err of Coef.	0.690

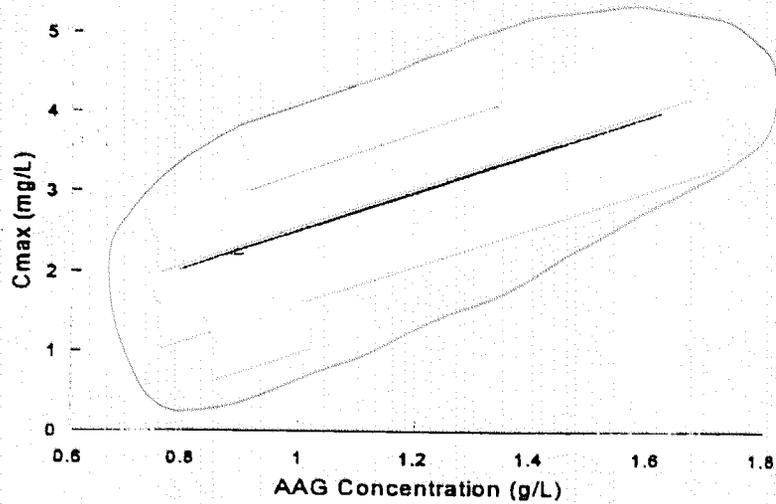
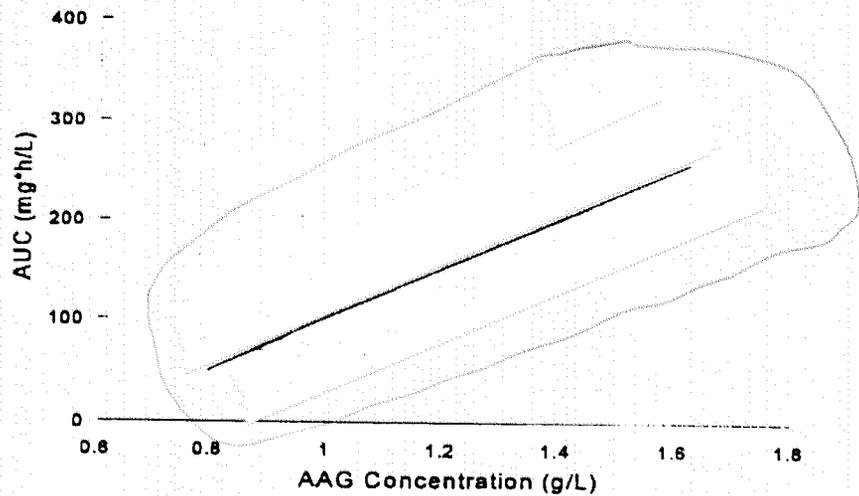


Figure 16. Correlation Between Plasma AAG and Mifepristone AUC (single 600 mg dose)

Regression Output	
Intercept	-145.31
Std Err of Y Est	47.26
R <sup>2</sup>	0.563
Slope	247.12
Std Err of Coef.	51.27

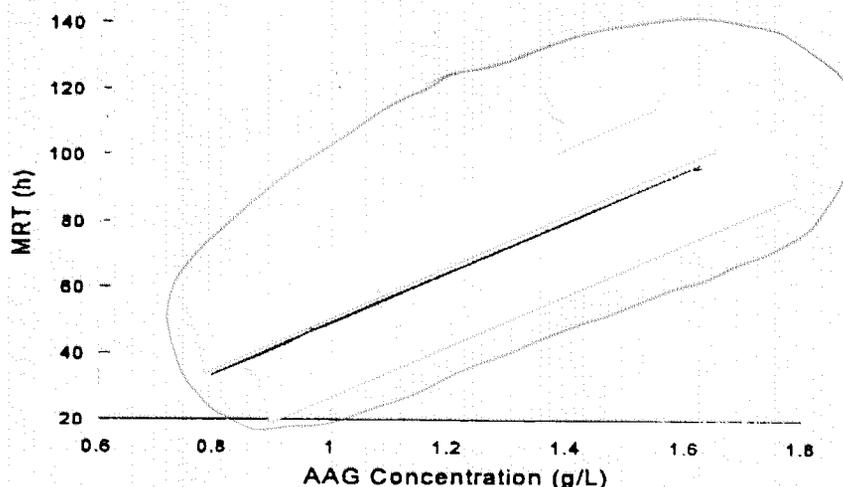


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Figure 17. Correlation Between Plasma AAG and Mifepristone MRT (single 600 mg dose)

Regression Output

Intercept	-28.70
Std Err of Y Est	14.75
R <sup>2</sup>	0.568
Slope	77.84
Std Err of Coef.	16.00



The efficacy, in terms of success in termination of pregnancy was also measured and is reported in Table 22. It appears that a single mifepristone dose of 600 mg is approximately 85% effect in facilitating abortion in these 20 pregnant females. According to the package insert, however, a single 600 mg dose of mifepristone is  effective.

Table 22.

Mefipristone 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

**Sponsor's Conclusions:**

1. No significant difference was observed in terms of the dose. The pharmacokinetic parameters of RU 38 486 and RU 42 633 were different, but their concentrations had the same profile.

2. Cmax and AUC were positively correlated with the concentration of AAG. After administration of a high dose (400-600 mg) of RU 38 486 the binding capacity of AAG was exceeded. Cmax was limited by the concentration of AAG and did not increase with the dose. The clearance (Cl) was increased, which restricted the increase in AUC with the dose. The increase in the volume of distribution (Vd) was even greater, hence an initially slow elimination which became more rapid at the later time points when the amount of the products present in the organism was sufficiently reduced for Vd and Cl to return to normal values, AAG no longer being saturated.

**Reviewer Comments:**

1. I concur with the sponsor's conclusions from the pivotal pharmacokinetic/pharmacodynamic study, 87/486/15. It is very apparent that the binding of RU 38 486 and RU 42 633 to AAG is a significant factor in the pharmacokinetics of these compounds.
2. It should also be noted that the 600 mg dose of RU 38 486 was only 85% effective in the termination of pregnancy, which is obviously lower than the [ ] efficacy claim that exists in the proposed package insert. Obviously, the number of subjects (20) in study 87/486/15 is limited and the [ ] efficacy rate has probably been derived from large clinical studies although these data have not been submitted to the Division of Pharmaceutical Evaluation II.

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APPENDIX IV  
*"Supportive" Pharmacokinetic Studies*

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AM 53

87/466/CN

87/517/CN

87/627/CN

85/486/04

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**Study Number:** 86/318/CN

**Study Title:** Absolute Bioavailability of RU 38 486. Preliminary Study in Man

**Study Dates:** May, 1986 - June, 1986

**Study Director:**

**Study Design:** Randomized, cross-over study

**Study Population:** Four healthy male volunteers, aged 28-30 (28.8 mean)

**Study Drug:** RU 38 486 administered in a single 40 mg dose by IV injection (40 mg in 100 ml of 0.9% saline infused over one hour) or orally in 150 ml of water

**Statistical Methodology Employed:**

The pharmacokinetic analysis included calculation of the usual parameters after mathematical modeling. Analysis of the pharmacokinetic parameters was done by analysis of variance taking into account the repetition of measurements in the same subject and the order of administration of the compound.

**Results:**

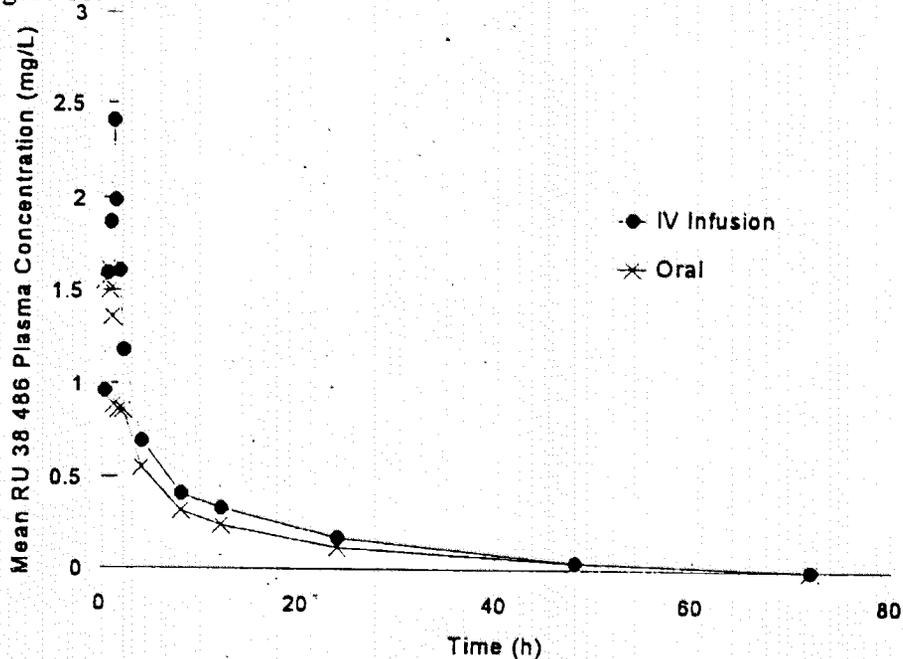
The pharmacokinetic parameters from 40 mg doses (IV and PO) to normal healthy males are presented in Table 23.

Table 23.

Subject #		1	2	3	4	Mean ± SEM
IV	Cmax (mg/L)	[				2.41 ± 0.35
	Tmax (h)					-
	t½ (h)					11.4 ± 1.5
	AUC (mg×h/L)					14.3 ± 2.5
PO	Cmax (mg/L)	]				1.88 ± 0.39
	Tmax (h)					0.44 ± 0.12
	t½ (h)					11.0 ± 2.6
	AUC (mg×h/L)					10.7 ± 2.7
F (%)						72 ± 9

The mean plasma concentration versus time profiles for each treatment are included in Figure 18.

Figure 18.



### Conclusions:

The absorption of RU 38 486 after oral administration was very rapid ( $T_{max} = 0.4$  hours).

The terminal  $T_{1/2}$  of 11.2 hours was unusually short.

The bioavailability of a 40 mg oral dose of RU 38 486 is  $\approx 72\%$  compared to a 40 mg given by IV infusion (1 h infusion time).

### Reviewer Comment:

A 40 mg dose given to male volunteers does not appear to have the multiple phase elimination that has been observed in the female study subjects with higher doses (see Study 87/486/15).

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**Study Number:** AQ 00  
**Study Title:** RU 38 486 Human Pharmacokinetics (Pharmacokinetics and Metabolism in Man after Intravenous Administration)  
**Study Dates:** Not specified (report dated December 22, 1983)  
**Study Director:**   
**Study Design:** Uncontrolled study  
**Study Population:** Three healthy, male volunteers

**Study Drug:**

Tritiated RU 38 486 in either:

Injectable form: The compound (25  $\mu$ Ci - 286 ng) dissolved in 0.9% sodium chloride,

or,

Oral form: Two tablets, each containing 50 mg of active ingredient with an activity of 25  $\mu$ Ci

**Statistical Methodology Employed:**

Mathematical adjustment of the curves to a kinetic model was done by computer using the non-linear regression program

**Results:**

After either IV or oral administration, the plasma kinetics corresponded to an open two-compartment model. After IV administration, the  $\alpha$  distribution half-life was 1 hour and the  $\beta$  elimination half-life, 12 hours. The volumes of distribution were very small ( $V_c = 8$  L and  $V_{dss} = 1$  L). After oral administration, the  $\alpha$  distribution half-life was also 1 hour, but the  $\beta$  elimination half-life was 24 hours. The volumes of distribution were greater than previously ( $V_c = 45$  L and  $V_{dss} = 100$  L). The peak plasma concentration of RU 38 486, about 2% of the dose per liter, was observed one hour after administration of the tablets. Urinary and fecal excretion of radioactivity was virtually complete. Urinary excretion was 9% for both routes of administration.

Overall, the study drug is well absorbed. Its absolute bioavailability is low (30-56%) due to first pass effect. The  $\beta$  Elimination half-life was slow.

The bioavailability of RU 38 486 varies fairly considerably from one subject to another, since the areas under the plasma kinetics curves or the value of the peak concentration vary by a factor of more than 2 between subjects.

**Reviewer Comments:**

The low bioavailability of RU 38 486 observed in this study is not confirmed in the other PK study conducted in male volunteers (86/318/CN) in which a F of  $\approx 0.7$  was observed.

**Study Number:** AM 53  
**Study Title:** RU 38 486 Preliminary Pharmacokinetics - Study in Humans  
**Study Dates:** Not specified (report prepared July, 1982)  
**Study Director:**   
**Study Design:** Uncontrolled study  
**Study Population:** Four healthy, well-informed volunteers (3 male, 1 female), aged 23-29 years  
**Study Drug:** Tritiated RU 486 administered either by IV (12.5  $\mu$ Ci, 140 ng in 3 ml of saline) or orally (6.25  $\mu$ Ci, 70 ng in 250 ml of water)

**Preliminary Evaluation Parameters:**

Determination of initial pharmacokinetic parameters in humans using radioactive RU 486.

**Statistical Methodology Employed:**

All plasma concentrations versus time profiles were fitted to a sum of exponentials using a Fortran program.

**Results:**

The distribution phase is rapid ( $T_{1/2} = 0.5$  hr.). The elimination phase for RU 38 486 has a  $T_{1/2}$  of 16 hours for total radioactivity. The apparent initial volume of distribution is estimated to be small (about 7 liters). At equilibrium the volume of distribution is also small (2 liters). Urine is a minor route of excretion accounting for only 10-15% of the administered radioactivity over 60-72 hours.

The parent compound, RU 38 486 accounts for 90% of radioactivity in plasma 15 minutes post dose and 23% after 24 hours following IV administration. After oral administration, 40% of radioactivity is RU 38 486 at 1 hour and 11% after 24 hours. Thus confirming the first pass metabolism of RU 38 486.

Seven metabolites of RU 38 486 were identified.

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**Study Number:** 87/466/CN  
**Study Title:** Bioavailability of 4 Formulations in Healthy Male Volunteers  
**Study Dates:** Not specified (report dated July 9, 1987)  
**Study Director:** [REDACTED]  
**Study Design:** Open, randomized, cross-over study  
**Study Population:** Twelve fasted, healthy male volunteers aged from 19 to 24 years (21.42 mean)  
**Study Drug:** One single dose of 50 mg of RU 486 in 4 treatments

**Preliminary Evaluation Parameters:**

Pharmacokinetic and statistical analysis of the bioavailability of study drug in four treatments which differed either in [REDACTED] of the active ingredient or in the manufacturing process.

**Statistical Methodology Employed:**

The pharmacokinetic parameters for each product were subjected to a 2-way analysis of variance with calculation of the mean, variance and standard error of the mean of the parameters for each factor. Where the analysis of variance showed a significant treatment effect, the means of the parameters in terms of the treatment were compared with one another by Tukey's t test, using the residual variance of the analysis of variance. Westlake's confidence interval was calculated using residual variance of the analysis of variance and taking each treatment successively as the reference.

**Results:**

Pharmacokinetic and statistical analysis showed that [REDACTED] tended to reduce the amount of RU 38 486 absorbed, thereby justifying [REDACTED]. The third treatment, was an identical tablet to that prepared with the second, produced a tablet from which the absorption of RU 38 486 was quantitatively similar but slower. Different batches of active ingredient incorporated in tablets of identical manufacture therefore produced tablets of differing bioavailability. [REDACTED] with the [REDACTED] mixture of the granulate prepared with the third treatment of active ingredient eliminates this difference and ensures the production of bioequivalent tablets.

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**Study Number:** 87/517/CN

**Study Title:** Bioequivalence Study of 4 Dosage Forms of RU 38 486 Administered Orally to Healthy Male Volunteers

**Study Dates:** September 1986 - November 1986

**Study Director:** \_\_\_\_\_

**Study Design:** Open, randomized, cross-over study in a Latin square design

**Study Population:** Eight fasted, healthy male volunteers, aged from 22 to 32 years (27.4 mean)

**Study Drug:** RU 38 486 in a single dose of 200 mg, in 4 treatments in a 20 ml solution, 4 x 50 mg tablets or 1 x 200 mg tablet a: 20 ml of a 10 mg/l solution, batch \_\_\_\_\_ 20966-101 b: 4 x 50 mg tablets, batch \_\_\_\_\_ 20780-147 c: 1 x 200 mg tablet, batch \_\_\_\_\_ 20780-32 d: 1 x 200 mg tablet, batch \_\_\_\_\_ 21236-12

**Preliminary Evaluation Parameters:**

Statistical and pharmacokinetic comparison of the bioavailability of the study drug administered in an oral solution or tablet form

**Statistical Methodology Employed:**

3-way analysis of variance (treatment, subject, period); where the analysis of variance showed a significant treatment effect, the means of the parameters for each treatment were compared with one another by Tukey's t-test using the residual variance of the analysis of variance. Westlake's confidence interval for the C<sub>max</sub>, AUC, and MRT obtained after treatments was calculated using the residual variance of the analysis of variance and taking each tablet in turn as the reference.

**Results:**

RU 38 486, administered in the form of a solution, was more rapidly absorbed than in tablet form, although absorption was rapid in all cases. This difference between solution and tablet yields plasma concentrations which follow a different time course for the solution and the tablets and makes a comparison between the AUC obtained with the solution and the tablets difficult because of the non-linear kinetics of RU 38 486 in a dose of 200 mg.

Conversely, the plasma concentrations obtained after administration of the tablets were very similar and none of the pharmacokinetic parameters studied showed a significant difference in terms of the tablet administered. The results obtained with the tablets may therefore be compared despite the lack of linearity of the kinetics.

The different types of tablets tested in this study are bioequivalent and may therefore be used without distinction clinically.

Table 24 outlines the PK parameters from each dosage form.

Table 24

Parameters	Product	Oral Mifepristone Treatment			
		A	B	C	D
		20 ml solution	4×50 mg tablets	1×200 mg tablet	1×200 mg tablet
C <sub>max</sub> (mg/L)	RU 38 486	2.39±0.23	1.81±0.32	1.87±0.18	1.77±0.23
	RU 42 633	1.93±0.19	1.46±0.26	1.39±0.18	1.24±0.16
T <sub>max</sub> (h)	RU 38 486	0.81±0.14	0.81±0.13	0.81±0.10	0.81±0.16
	RU 42 633	1.41±0.17	1.91±0.60	1.78±0.35	2.28±0.63
AUC (mg×h/L)	RU 38 486	24.0±2.2	24.4±2.1	31.1±3.9	25.8±2.2
	RU 42 633	46.2±4.9	39.1±4.4	44.1±4.7	38.3±3.3
MRT (h)	RU 38 486	21.4±0.9	26.5±1.7	26.9±1.7	27.0±1.3
	RU 42 633	24.4±0.8	28.6±1.6	29.9±1.9	30.0±1.3
t <sub>1/2</sub> (h)	RU 38 486	14.5±0.8	15.6±1.3	17.1±1.3	16.8±1.6
	RU 42 633	18.2±0.9	19.6±1.8	21.1±2.0	21.0±1.6

**Reviewer Comment:**

Comparing the absolute bioavailability of the 200 mg tablets (treatments C and D) with 200 mg solution (treatment A), it appears that the  $F_{\text{absolute}} \approx 1.0$

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**Study Number:** 87/627/CN

**Study Title:** Study of the Relative Bioavailability of RU 38 486 Administered in the Form of a Rapid Release Vaginal Tablet Compared with the 400 mg Oral Tablet

**Study Dates:** November 1986 - February 1987

**Study Director:** [REDACTED]

**Study Design:** Open, randomized cross-over study

**Study Population:** Four non-pregnant healthy female volunteers 31 to 37 years of age

**Study Drug:** Single 400 mg dose of RU 38 486, administered orally (2 x 200 mg oral tablets) batch 21236-12, or vaginally (1 x 400 mg vaginal tablet) batch 21236-38

**Preliminary Evaluation Parameters:**

Measurement of bioavailability of the rapid release vaginal tablets compared with the oral tablets, used as reference. Plasma concentrations were assayed by [REDACTED] after separation by [REDACTED]

**Statistical Methodology Employed:**

The means and standard errors of the mean of the concentrations were calculated for each product assayed after each treatment as a function of the sampling time.

**Results:**

The concentrations after vaginal administration were either not measurable or very low, whereas after the oral route they were high, of rapid onset, and persisted until the last sampling time (96 hr).

The bioavailability of the rapid release vaginal tablets is therefore practically zero compared with the oral tablets.

As the rapid release vaginal tablet disintegrates rapidly *in vitro*, it is apparent that this route of administration does not yield high plasma concentrations.

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**Study Number:** NL/86/486/04  
**Study Title:** Pharmacokinetics of Delivery of RU 38 486 (Mifepristone) as Vaginal Suppositories (Placebo, 10 mg, 25 mg, and 50 mg per Suppository) in Normal Women: A Pilot Study  
**Study Dates:** Not specified (report dated September 2, 1986)  
**Study Director:** [REDACTED]  
**Study Design:** Open label study  
**Study Population:** Eight healthy women volunteers  
**Study Drug:** RU 38 486 (10 mg, 25 mg, or 50 mg suppositories)

**Preliminary Evaluation Parameters:**

Tolerance measured from reported adverse events from subjects. Laboratory tests performed before and 48 hours after study drug administration.

Plasma concentration of RU 38 486 was assayed by a [REDACTED]

**Results:**

Study drug vaginal capsules are well tolerated. No serious subjective or objective adverse reactions are seen.

Degradation of the vaginal capsule is apparently very slow and variable resulting in a very late and inconsistent absorption of the active compound. A clear rise in plasma level is only seen 4-6 hours after drug application. In 8 of 9 cases a marked rise in plasma level is observed between 24 and 48 hours. It is unclear whether a peak level is reached before or after 48 hours.

This very long slow rise in plasma level makes it impossible to calculate AUC's, Tmax, and Cmax during the 48 hours sampling time as used in the study.

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**ATTACHMENT I**  
**Proposed Product Label**

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Labeling