CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS

FILING MEMO

Date: April 17, 1996

Time: 1:00 P.M.

Place: [redacted]

To: [redacted]

From: [redacted]

RE: 45-Day Filing Meeting
NDA 20-687, Mifepristone Tablets, 200 mg

Background:

Mifepristone (11β-[4-Dimethylaminophenyl]-17β-hydroxy-17α-[1-propynyl]-estra-4,9-dien-3-one) is a synthetic steroid that competes with progesterone at the progesterone receptor thus eliciting anti-progestational action. This action manifests itself as menstrual bleeding, disruption of placental function and disruption of the inhibitory effects of progesterone on the myometrial stimulatory effects of the prostaglandins.

The proposed indication is for the termination of intrauterine pregnancy through 49 days gestational age (Day 1 = first day of last menstrual period, confirmed clinically).

The advantages medical abortion provides over surgical methods include avoidance of risks associated with anesthesia, possibility of uterine perforation and cervical canal injury.

Mifepristone was developed by Roussel Uclaf (Paris, France) and has been approved and marketed by Roussel Uclaf in the countries outlined in Table 1. It is also reported that the product has not been withdrawn from any country for any reason related to safety or efficacy. In 1983, IND applications were made by The Population Council for the use of mifepristone as an abortifacient (I[redacted]) and in [redacted] (I[redacted]) in the US.

Table 1:

Country	Trade name	Date of Approval	Initial Date of Marketing
China	Xi Bai Lu	10/88	Not Marketed
France	Mifegyne®	12/88	9/89
United Kingdom	Mifegyne®	7/91	7/91
Sweden	Mifegyne®	9/92	10/92

The proposed recommended dosage regimen is; DAY 1: 600mg mifepristone (3x200mg tablets) in a single oral dose; DAY 3 (if abortion is NOT clinically confirmed): 400μg misoprostol (2x200μg tablets).

Reportedly, no unexpected adverse events were experienced at doses as high as three fold the recommended dose of mifepristone.

It is reported that termination of pregnancy is observed in ≈95% of the patients who have received the recommended dose of mifepristone and misoprostol.

Seven metabolites of mifepristone have been identified. The main metabolic routes of elimination are reportedly N-demethylation and terminal hydroxylation.

RU 38 486 (mifepristone) and metabolite, RU 42 633, are approximately 95% bound to a single high-affinity binding site on α_1-acid glycoprotein (AAG). The binding of both compounds is saturable at the plasma concentration of AAG. *In Vitro* testing indicated that RU 39 486 and RU 42 633 not bound to AAG binds in a non-saturable manner to human serum albumin.

The product is an immediate release tablet. The formulations used in the pharmacokinetic studies are included in Table 2.

Table 2: Formulation Summary

Ingredient	Role	Formulation		
		A	B	C
Mifepristone	Active principle			200 mg
Colloidal silica anhydrous				
Maize starch				
Microcrystalline cellulose				
Povidone				
Magnesium stearate				
TOTAL MASS of Tablet				

Formulation C is the proposed to-be-marketed formulation.

There are a total of 14 studies contained in Section 6 of the NDA submission; three in vitro studies; one assay technique study; nine pilot studies; and one large pharmacokinetic study (40 evaluable patients) in pregnant women. The summary of the *in vivo* studies is included in Table 3.

Table 3: Study Summary

Pilot Studies				
Study #	Design	N	Dose	Formulation
87/593/CN	Open-label, non-pregnant subjects	10F	600 mg	
87/601/CN	Open-label, non-pregnant subjects	4F	600 mg tritiated	
87/592/CN	Open, randomized, cross-over in non-pregnant subjects	10F	20mg IV 20mg PO	
86/257/CN	Randomized, uncontrolled, open, cross-over, in non-pregnant subjects	12F	50mg 150mg 450mg	
86/318/CN	Randomized, Cross-over	4M	40mg IV 40mg PO	
AQ 00	uncontrolled	3M	280ng IV 100mg PO	
AM 53	uncontrolled in non-pregnant subjects	1F 3M	140ng IV 50mg PO	
87/466/CN	open-randomized, cross-over	12M	50mg	
87/517/CN	bioequivalence open-randomized, cross-over	8M	50mg 200mg	
87/627/CN	cross-over study comparing vaginal and oral tablets	4F	400mg vaginal 400mg PO	
NL85/486/04	PK vaginal capsule	8F	0, 10, 25 or 50mg vaginal	
Pivotal PK Study				
Study #	Design	N	Dose	
S87/486/15	Open, randomized, uncontrolled, in pregnant subjects,<49 day of amenorrhea	40F	400 or 600mg	

In a radiolabelled study (87/486/CN), where 600 mg mifepristone was given orally, 92.3 ± 0.8% (mean ± SEM, N=4) of the dose was accounted for eleven days post dose (83.1 ± 1.9% in feces and 9.2 ± 1.1% in urine). Elimination of the dose was not complete in this time frame since less than 0.4% of the dose was measured in the feces on Day 11.

Table 4 contains a summary of the pharmacokinetic data generated from the pivotal pharmacokinetic study (S87/486/15). Probably due to saturable protein binding, it is apparent that linear kinetics are not exhibited between doses of 400 and 600 mg. However, no dose adjustment is recommended in the proposed product labeling (single dose of 600 mg).

Table 4:

Pharmacokinetic Parameter (mean ± SEM)	400 mg Mifepristone (n=20)		600 mg Mifepristone (n=20)	
	RU 38 486	RU 42 633	RU 38 486	RU 42 633
Tmax (h)	1.25 ± 0.12	3.2 ± 1.1	1.45 ± 0.14	3.25 ± 0.41
Cmax (mg/L)	2.70 ± 0.23	2.07 ± 0.14	2.56 ± 0.18	2.182 ±0.091
AUC (mg×h/L)	78.7 ± 8.0	96.6 ± 8.9	106 ± 16	130 ± 17
MRT (h)	39.5 ± 2.6	43.6 ± 3.0	50.5 ± 4.9	52.4 ± 5.8
mean AAG (g/L)	1.06		1.02	

The dissolution specification for the drug product is that the mean percentage of active principle dissolved (n=6) after [redacted] minutes is not less than [redacted]. The dissolution method is approved by the European Pharmacopeia.

DISSOLUTION METHOD

Apparatus:
Dissolution Medium:
Volume:
Number of containers:
Tablets per container:
Rotation Speed:
Temperature:

[redacted]

RU 38 486 and its monodemethylated metabolite, RU 42 633 were isolated by [redacted] using [redacted] as the solvent. The extract was [redacted] by [redacted] on a [redacted] The average recovery of RU 38 486 was 96.7 ± 2.6%.

Sensitivity: 0.01 mg/L for a 0.3 ml sample

Specificity: No interfering [redacted] were observed in blank plasma and other possible metabolites have a much shorter retention time than the analytes of interest.

Accuracy (ranges of differences from theoretical values):

Within Day: RU 38 486: [redacted]
RU 42 633: [redacted]

Between Day: RU 38 486: [redacted]
RU 42 633: [redacted]

Precision (coefficients of variation limits):

Within Day: RU 38 486: [redacted]

	RU 42 633:	[redacted]
Between Day:	RU 38 486:	
	RU 42 633:	

The proposed labeling is included in Attachment I and the study summaries are included in Attachment II.

Comments:

1. The Pharmacokinetics/Metabolism 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. It is stated in the proposed package insert that, "drugs known to cause enzyme induction may reduce the efficacy of (mifepristone) due to increased metabolism." However, a full investigation of the enzymes involved in the metabolism of mifepristone is not submitted and an extensive search of the biomedical literature did not yield this information, although P450 3A has been strongly implicated. It is recommended that *in vitro* studies be carried out to fully identify the enzymes that catalyze the metabolism of mifepristone.

3. There is evidence that the inductive properties of known P-450 inducers are blocked by mifepristone (P.M.Shaw, M.Adesnik, M.C.Weiss and L. Corcos. The Phenobarbital-Induced Transcriptional Activation of Cytochrome P-450 Genes is Blocked by the Glucocorticoid-Progesterone Antagonist RU486. *Molecul Pharmacol.* 1993; 44: 775-783). Therefore, in cases where dose adjustment of another compound has been made to account for the induction of P-450, patient monitoring and/or dose re-adjustment may be warranted.

Recommendation:

It is recommended that, on the basis of the biopharmaceutical information provided, this submission is fileable. However, the comments above should be communicated to the sponsor as appropriate.

cc: [redacted] drug file, chron. files.

The attachments are being retained in the Division of

Pharmaceutical Evaluation II.

JUL 8 1996

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA: 20-687

Compound: Mifepristone Tablets, 200 mg

Submission Date: 3/14/96

Sponsor: The Population Council

Type of Submission: Original NDA

Code: 1P

Reviewer: [redacted]

I. SYNOPSIS

Mifepristone (11β-[4-Dimethylaminophenyl]-17β-hydroxy-17α-[1-propynyl]-estra-4,9-dien-3-one)is a synthetic steroid that competes with progesterone at the progesterone receptor thus eliciting anti-progestational action. This action manifests itself as menstrual bleeding, disruption of placental function and disruption of the inhibitory effects of progesterone on the myometrial stimulatory effects of the prostaglandins.

The proposed indication is for the termination of intrauterine pregnancy through 49 days gestational age (Day 1 = first day of last menstrual period, confirmed clinically). The advantages medical abortion provides over surgical methods include avoidance of risks associated with anesthesia and the possibility of uterine perforation and cervical canal injury. The sponsor states that termination of pregnancy is observed in ≈95% of the patients who have received the recommended dose of mifepristone and misoprostol, although these data have not been submitted to the Division of Pharmaceutical Evaluation II.

The proposed recommended dosage regimen is;

DAY 1 600 mg mifepristone (3×200 mg tablets) in a single oral dose;

If abortion is NOT clinically confirmed;

DAY 3 400 µg misoprostol (2×200 µg tablets).

Reportedly, no unexpected adverse events were experienced at doses as high as three fold the recommended dose of mifepristone.

There are a total of 14 studies contained in Section 6 of the NDA; three *in vitro* studies; one assay technique study; nine pilot studies; and one pivotal pharmacokinetic/pharmacodynamic study in pregnant women (40 evaluable patients).

II. Comments

Comments 1 and 2 were communicated by the Division of Metabolism and Endocrin Drug Products [redacted] to the Population Council in a letter

dated May 20, 1996 and Comments 2 and 3 were communicated to the sponsor on June 20, 1996.

1. The "Pharmacokinetics/Bioavailability" 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. It is stated in the proposed package insert that "drugs known to cause enzyme induction may reduce the efficacy of (mifepristone) due to increased metabolism." However, a full investigation of the enzymes involved in the metabolism of mifepristone was not submitted and an extensive search of the biomedical literature did not yield this information. If this information is available, it is recommended that it be submitted to the Agency. Alternatively, it is suggested that *in vitro* studies be carried out to fully identify the enzymes that catalyze the metabolism of mifepristone.

3. To support the rationale for using the dissolution medium and volume plus the selected [redacted] for the proposed dissolution method, the following information should be provided:

   a) pH solubility data for mifepristone
   b) [redacted] condition information at [redacted] for various media
   c) Tablet dissolution profiles (including raw data and mean data) in various media (i.e., simulated gastric fluid, simulated intestinal fluid and a range of pH's representative of physiological conditions) that provide adequate sink conditions with appropriate sampling times to characterize the profile
   d) Raw data and profiles at different [redacted] in the aforementioned various dissolution media.

4. The reported assay and assay validation used to assess plasma mifepristone levels are appropriate and are accepted by the Office of Clinical Pharmacology and Biopharmaceutics.

III. RECOMMENDATION

NDA 20-687 submitted on March 14, 1996, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the sponsor has provided appropriate information to satisfy the clinical pharmacology and biopharmaceutic regulations outlined in CFR 21.320.

- The proposed dissolution method and specifications are acceptable on an interim basis. However, additional dissolution data is needed to satisfy OCPB/DPE II requirements (see Comment 3).

- The proposed package insert should be updated as appropriate to incorporate the changes recommended in the Agency's letter dated May

20, 1996. The sponsor is reminded that the pharmacokinetic parameters contained in the proposed package insert should be reported as mean ± standard deviation, not mean ± standard error of the mean as is reported in Section 6 of the NDA.

- It should be noted that the catalytic enzymes in the metabolism of RU 38 486, the antiprogesterone activity of the metabolites and the protein binding in pregnant women have not been adequately characterized/reported. However, since the proposed indication utilizes a single dose of mifepristone, these data are of less importance. If future indications are sought which include these data will be of great importance and proper characterization will be necessary.

The Recommendation and Comment 3 should be communicated to the sponsor as appropriate.

/S/

RD initialed by 6/4/96

FT signed by 151 7/8/96

Biopharm Day, June 10, 1996, Attendees:

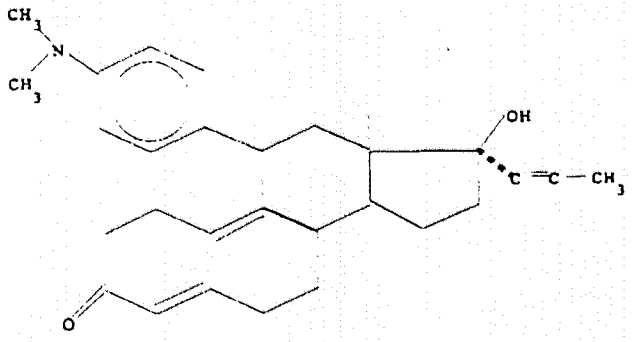
cc:

APPEARS THIS WAY
ON ORIGINAL

TABLE OF CONTENTS:

IV. BACKGROUND

RU 38 486 (mifepristone) is a synthetic steroid. The chemical structure is as follows:



Mifepristone has been shown to have potent antiprogesterone and antiglucocorticoid activity and weak antiandrogenic activity without exhibiting progestomimetic, glucocorticoid, or androgenic agonist activity. Its antiprogesterone activity opposes the maintenance of pregnancy.

Clinically, mifepristone constitutes a medical alternative to uterine aspiration for the termination of intrauterine pregnancies of ≤63 days of amenorrhea. For this indication, a single oral dose of 600 mg mifepristone followed 48 hours later with a single oral dose of 400 µg misoprostol has been selected.

Mifepristone was developed by Roussel Uclaf (Paris, France) and has been approved and marketed by Roussel Uclaf in the countries outlined in Table 1. It is also reported that the product has not been withdrawn from any country for any reason related to safety or efficacy. In 1983, IND applications were made by The Population Council for the use of mifepristone as an abortifacient (IND [redacted] and in [redacted] (IND [redacted] in the US.

Table 1:

Country	Trade name	Date of Approval	Initial Date of Marketing
China	Xi Bai Lu	10/88	Not Marketed
France	Mifegyne®	12/88	9/89
United Kingdom	Mifegyne®	7/91	7/91
Sweden	Mifegyne®	9/92	10/92

V. Formulation and Administration

The product is an immediate release tablet. The formulations used in the pharmacokinetic studies are included in Table 2. It should be noted that, Formulation C is the formulation marketed in Europe and the proposed to-be-marketed formulation in the U.S.

Table 2: Formulation Summary

Ingredient	Role	Formulation		
		A	B	C
Mifepristone	Active principle			200 mg
Colloidal silica anhydrous				
Maize starch				
Microcrystalline cellulose				
Povidone				
Magnesium stearate				
TOTAL MASS of Tablet				

The proposed administration of mifepristone is three 200 mg tablets for total single oral dose of 600 mg, on Day 1. On Day 3, if termination of the pregnancy is not confirmed, then a single, 400 µg, oral dose of misoprostol will be administered. The patient will be monitored on Day 3 and return to the clinic on Day 14, if the termination of the pregnancy is not confirmed at these times, a surgical abortion will be performed.

VI. *In Vitro* Methodology

Dissolution Testing

The following *in vitro* dissolution method and specifications are proposed to be used for the release of batches of mifepristone in the US.

DISSOLUTION METHOD (approved by the European Pharmacopeia)

Apparatus
Dissolution Medium
Volume
Number of containers
Tablets per container
Rotation Speed
Temperature

SPECIFICATIONS (USP XXIII)

The USP XXIII acceptance criteria with Q= after minutes will be used (see Table 3).

Table 3

Mean dissolution profile of bio-lots used in three pharmacokinetic studies by the method listed above is presented in Table 4, below (raw data were not submitted). It should be noted that in all cases of RU 38 486 is in solution by minutes.

Table 4

Lot #	21236-50 (n=5) Study 87/486/15			20780-32 (n=6) Study 85/517/CN			21236-12 (n=5) Studies 87/517/CN and 87/593/CN		
	Range %	Mean %	%CV	Range %	Mean %	%CV	Range %	Mean %	%CV
5 min		70	1.6		60.4	9.7		76.3	5.6
10 min		94	1.5		94.8	3.4		97.9	0.7
15 min		98	1.3		101.8	1.7		101.3	0.2
30 min		101	1.1		102.5	1.7		102.4	0.2
45 min		101	1.1		102.7	2.2		102.4	0.2
60 min		101	1.1		103.1	2.1		102.4	0.3

Reviewer Comments:

A. The dissolution data submitted are less than adequate. Only mean and range dissolution data in one media has been submitted to NDA 20-687. Traditionally, OCPB/DPE II requires data (raw data with proper analyses) in various media, including simulated gastric fluids, simulated intestinal fluid and a range of pH's representative of physiological conditions, using the to-be-marketed formulation .

B. It is recommended that the speed used in the dissolution method be reduced from to provide a more rigorous, discriminating test of the dissolution properties of mifepristone.

C. The proposed dissolution method and specifications are accepted on an interim basis. However, development of an amended dissolution method incorporating Comment A, above, and submission of additional

dissolution data, Comment B, above, using 12 tablets/lot from 3 production size lots are required for full acceptance of the method.

VII. Analytical Methodology

Study 89/1243/CN describes the assay techniques and validation of RU 38 486 and its monodemethylated metabolite, RU 42 633 in human plasma. A

Reviewer Comment:

Overall, the validation of the used to assess plasma RU 38 486 and RU 42 633 is appropriate and the analytical method is accepted.

VIII. Pharmacokinetic/Pharmacodynamic Studies

The pharmacokinetic (absorption, distribution, metabolism and excretion) and pharmacodynamic characteristics of mifepristone were assessed in four pilot studies (87/593/CN, 87/601/CN, 87/592/CN and 86/257/CN), one pivotal study (S87/486/15) and seven supportive studies (86/318/CN, AQ 00, AM 53, 87/466/CN, 87/517/CN, 87/62 7/CN and 85/486/04) and additional information was gained from three *in vitro* studies (86/274/CN, 87/591/CN and 88/739/CN).

A. Pharmacokinetics

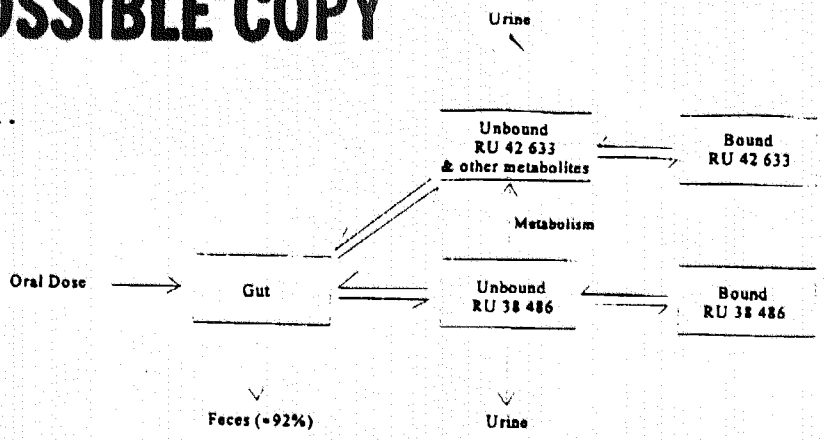
The proposed dosing of mifepristone is a single 600 mg dose, with no dose adjustment. Therefore, dose proportionality, multiple dose kinetics and various dosing regimens are irrelevant for the indication of abortifacient. Table 5 represents a summary of the pilot and supportive pharmacokinetic studies and the pivotal pharmacokinetic/pharmacodynamic study. Appendices II, III and IV include specific details on the study design, data analysis and the individual results of each study.

Table 5

Study #	Design	N	Dose	Page
Pilot Studies (Appendix II)				
87/593/CN	Open-label, non-pregnant subjects	10F	600 mg	26
87/601/CN	Open-label, non-pregnant subjects	4F	600 mg tritiated	29
87/592/CN	Open, randomized, cross-over in non-pregnant subjects	10F	20 mg IV 20 mg PO	32
86/257/CN	Randomized, uncontrolled, open, cross-over, in non-pregnant subjects	12F	50 mg 150 mg 450 mg	35
Pivotal PK Study (Appendix III)				
S87/486/15	Open, randomized, uncontrolled, in pregnant subjects,<49 day of amenorrhea	40F	400 or 600 mg	39
"Supportive" PK Studies (Appendix IV)				
86/318/CN	Randomized, Cross-over	4M	40 mg IV 40 mg PO	46
AQ 00	uncontrolled	3M	280 ng IV 100 mg PO	47
AM 53	uncontrolled in non-pregnant subjects	1F 3M	140 ng IV 50 mg PO	49
87/466/CN	open-randomized, cross-over	12M	50 mg	50
87/517/CN	bioequivalence open-randomized, cross-over	8M	50 mg 200 mg	51
87/627/CN	cross-over study comparing vaginal and oral tablets	4F	400 mg vaginal 400 mg PO	53
85/486/04	PK vaginal capsule	8F	10,25,50 mg vaginal	54

A proposed model that appears to most closely approximate the pharmacokinetics of mifepristone (although not tested) is outlined in Figure 1.

Figure 1.

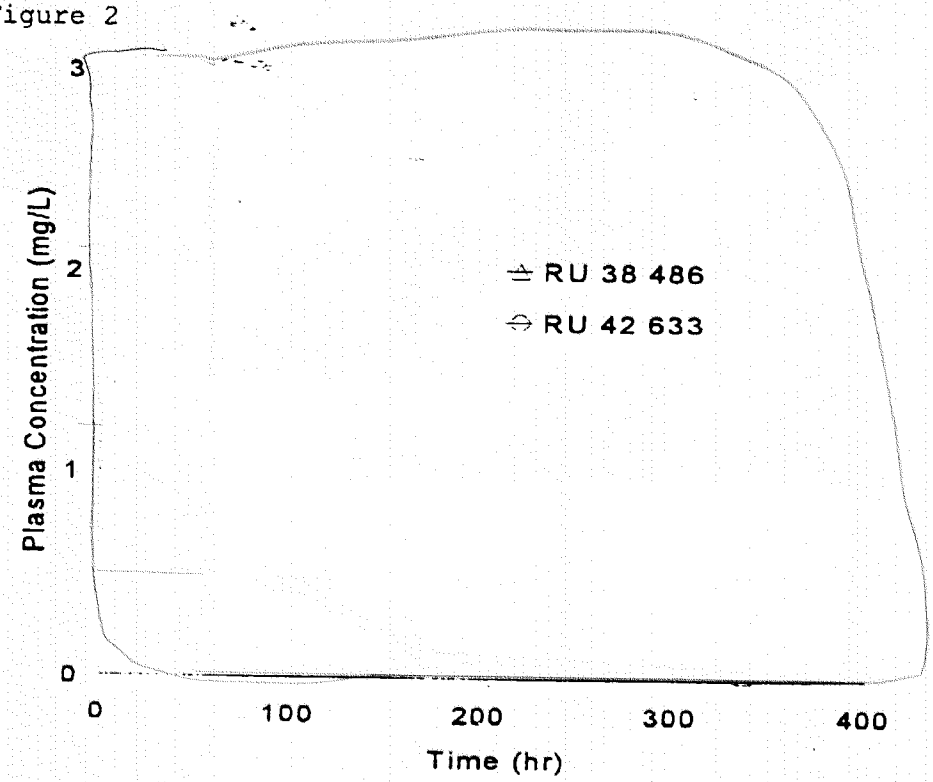


The pharmacokinetic parameters (mean ± standard deviation) derived from the pivotal pharmacokinetic/pharmacodynamic study in 20 pregnant women after a single oral dose of 600 mg of mifepristone are outlined in Table 6 and illustrated in Figure 2.

Table 6	RU 38 486	RU 42 633
Tmax (h)	1.45 ± 0.59	3.25 ± 1.8
Cmax (mg/L)	2.56 ± 0.78	2.16 ± 0.40
AUC (mg*h/L)	106 ± 68	130 ± 74
MRT* (h)	50.5 ± 21.2	52.4 ± 25.4

*MRT is calculated by AUMC/AUC. It should be noted that, since the kinetics of RU 38 486 is non-linear, the value MRT is not a true measure of the mean exposure to RU 38 486 over time and should be considered apparent MRT.

Figure 2



Absorption

Relative bioavailability

Results from study 87/517/CN indicate that mifepristone administered in solution form is more rapidly absorbed than in tablet form, but absorption is rapid in all cases. The $F_{relative}$ for RU 38 486 appears to be ≈1.

Reviewer Comment:

It should be noted that the 200 mg mifepristone dose used in study 87/517/CN is one-third the proposed clinical dose of 600 mg.

Absolute Bioavailability

A preliminary absolute bioavailability study in four male subjects (Report 86/318/CN) and a definitive absolute bioavailability study in 10 female subjects (Report 87/592/CN) were completed with mifepristone. The males received 40 mg mifepristone by the intravenous and oral (oral solution) routes, and the females received 20 mg mifepristone in the same manner. In both studies mifepristone was administered as a solution for both intravenous and oral dosing. The 20 mg dose was chosen in order to remain within the range of linearity of the pharmacokinetics of mifepristone.

After oral dosing with 20 and 40 mg mifepristone absorption was very rapid (Tmax = 0.6 and 0.4 hours, respectively).

The fraction of the dose absorbed into the body was calculated from the ratio of the AUCs after intravenous and oral treatment. The mean calculated F under these conditions was 0.69.

To allow for a variation in Cl between the two treatments due to a variation in AAG, Cl after oral treatment was calculated from the estimated volume of distribution as a function of AAG from the equation of the regression line determined after intravenous treatment and from the $t_{½}$ obtained after oral treatment. By this method the mean F = 0.66.

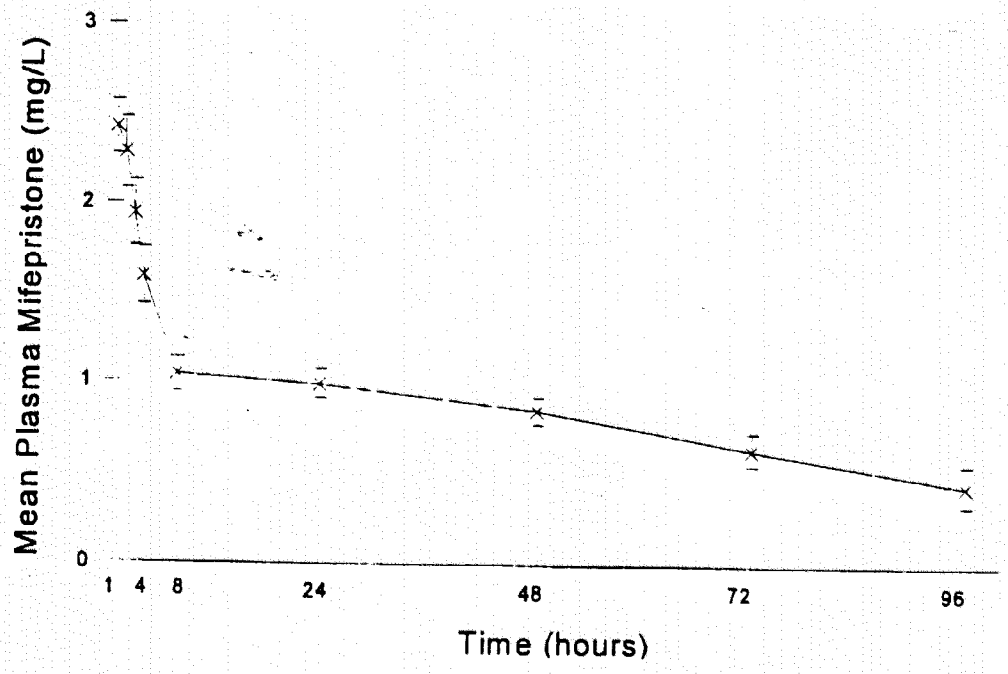
These results confirmed the results of the preliminary study in males, where F = 0.72.

Distribution

In Vitro Studies (Appendix I)				
86/274/CN	*In Vitro* Study of the Blood Binding of RU 38 486 in Man	-	Tritiated RU 38 486	19
87/591/CN	*In Vitro* Study of Binding of RU 38 486 and RU 42 633 to Human AAG and HSA	-	Tritiated RU 38 486 Tritiated RU 42 633	22
88/739/CN	*In Vitro* Study of Blood Binding of RU 42 633 in Man	-	Tritiated RU 42 633	23
87/570/CN	Study of Plasma Drug Interactions with RU 38 486, *In Vitro* Protein Binding	-	RU 38 486	24

The mean plasma concentration profile of mifepristone (± SEM) after the proposed dose to 20 pregnant females is represented in Figure 3. The sharp change in the elimination rate (at about 8 hours post-dose) is due to the saturable binding of mifepristone to α_1-acid glycoprotein (AAG). It should be noted that AAG levels do not rise significantly during pregnancy. However, these women had serum AAG levels slightly higher than normal (data not shown).

Figure 3. Pharmacokinetics of Mifepristone in 20 Pregnant females (Mean ± SEM)



As will be mentioned repeatedly in this review, RU 38 486 and its metabolite, RU 42 633 exhibit saturable binding to AAG. The excess drug not bound to AAG will bind non-saturably and relatively weakly to other plasma proteins. The association constants of the various plasma proteins tested (*In Vitro* binding study# 86/274/CN) are outlined in Table 7.

Table 7

	Protein (μM)	RU 38 486 binding (%)	# binding sites	K (M^{-1})	nK (M^{-1})
AAG	18.4	68.5	0.9 ± 0.02	$8\times10^6 \pm 0.5\times10^6$	$7.2\times10^6 \pm 0.5\times10^6$
HSA	600	9.9			32000 ± 438
VLDL	0.0792	1.3			$33\times10^6 \pm 2.5\times10^6$
LDL	1.52	2.7			$3.5\times10^6 \pm 0.09\times10^6$
HDL	14.8	12.2			$1.6\times10^6 \pm 0.08\times10^6$
Y Gb	87.5	4.9			$0.109\times10^6 \pm 0.007\times10^6$
RBC					NK=0.4 ± 0.008

The Vd of AAG is ≈5.5 L for a plasma concentration of AAG of 15.7 μM, since there is only one AAG binding site for mifepristone per AAG molecule, the binding capacity of AAG is about 90 μM, which is equivalent to 40 mg mifepristone. Therefore, a significant amount of free drug should be present in the blood after a 600 mg dose of mifepristone. It is possible from these data that the t½ of free drug is very short compared to that of the drug bound to AAG. Consequently, changes in absorption and/or presystemic metabolism of RU 38 486 will result in plasma levels above the expected Cmax, for a relatively short time. It should be noted however, that total AUC and Cavg will be proportionally higher in the aforementioned situation.

It is apparent from the graphs below (Figures 4, 5 and 6) 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.

Figure 4. Correlation Between Plasma AAG and RU 38486 Cmax (single 600 mg dose)

Regression Output	
Intercept	0.115
Std Err of Y Est	0.636
R^2	0.402
Slope	2.399
Std Err of Coef.	0.690

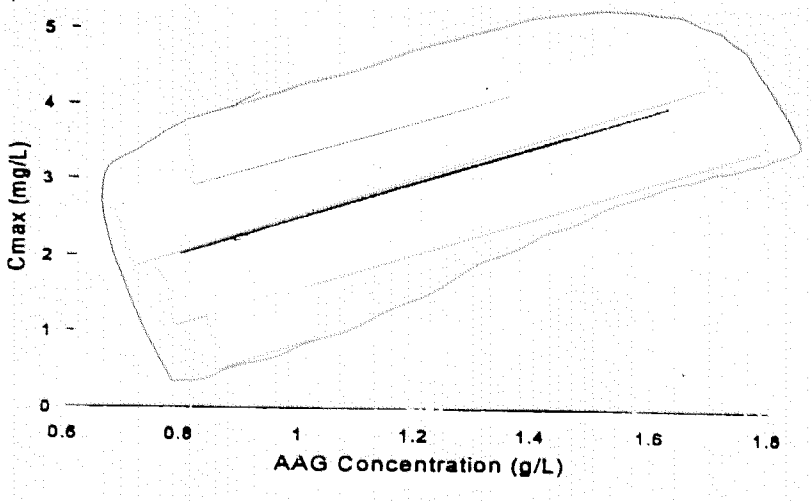


Figure 5. Correlation Between Plasma AAG and RU 38486 AUC (single 600 mg dose)

Regression Output	
Intercept	-145.31
Std Err of Y Est	47.26
R^2	0.563
Slope	247.12
Std Err of Coef.	51.27

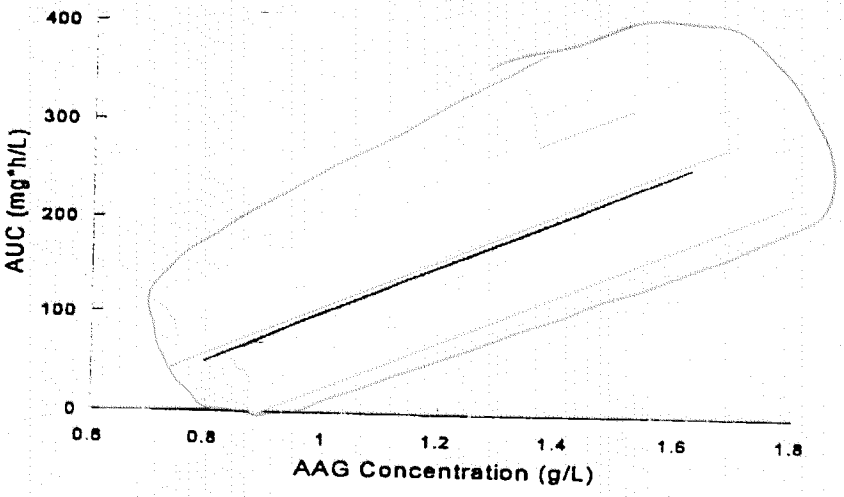
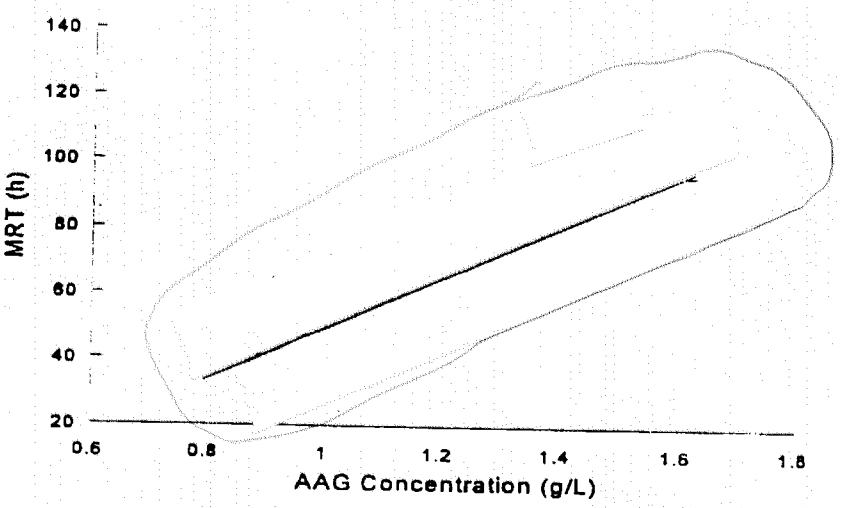


Figure 6. Correlation Between Plasma AAG and RU 38486 MRT (single 600 mg dose)

Regression Output	
Intercept	-28.70
Std Err of Y Est	14.75
R^2	0.568
Slope	77.84
Std Err of Coef.	16.00



Mifepristone is 98% bound to serum proteins, but binding to erythrocytes is negligible (<1%). The only serum protein that displays saturable binding is AAG, with one high-affinity site. As already mentioned, the primary metabolite, RU 42 633, also binds to AAG and competes with RU 38 486 for the single binding site.

Many of the clinical Phase 1 pharmacokinetic studies of mifepristone measured AAG in plasma by [redacted]. The mean concentrations of AAG were typically about 0.64 to 1.06 g/L (15 to 24 µM), within the normal limits for healthy young women.

The volume of distribution (Vd) and the clearance (Cl) of mifepristone were shown to be negatively correlated with AAG, with Vd and Cl being greater in subjects with low AAG concentrations. Conversely, the Cmax

and AUC were positively correlated with AAG, both after a 20 mg IV or oral dose and after a 600 mg oral dose.

Metabolism

Seven mifepristone metabolites have been mentioned in clinical trial reports. Current assay conditions of mifepristone by [redacted] in plasma have enabled three metabolites to be identified by virtue of their [redacted] properties, which are identical to those of the synthetically prepared reference products. These three metabolites are as follows: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11β; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

RU 42 633, the primary metabolite, was evaluated in nearly all of the studies. The plasma concentration profiles of mifepristone and RU 42 633 tend to be very similar, see Figure 7.

Figure 7. Plasma Concentrations of Mifepristone (parent compound and metabolites)