Valeuciennes Trial
7-1/5 to

EXH. 5

Protocol FF/92/486/24 with Case Record Forms

NDA 20-687

Volume 1.38

Pages 5 - 46, 90 - 115

(*Please Note*: the French version of the

protocol found on pages 47 - 89 is not included.)

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 4

CERTIFICATE OF INSURANCE OF

PROFESSIONAL CIVIL LIABILITY OF PERSONS INDICATED

APPEARS THIS WAY
ON ORIGINAL

[letterhead information]

CERTIFICATE OF INSURANCE OF

PROFESSIONAL CIVIL LIABILITY OF PERSONS INDICATED
by law No. 88.1138 of December 20, 1988 amended

certifies that the contract subscribed by ROUSSEL UCLAF, 35 Boulevard des Invalides - 75007 Paris, under NO. 6.746.570 B covers the Civil Liability of:

ROUSSEL SANTE R & D
102 route de Noisy
93230 Romainville

in their capacity as sponsor of biomedical research, and the liability of any person involved, pursuant to Article L.209.7 of the Public Health Code, in the study entitled:

- "Efficacy and safety of Mifepristone (RU 486) administered at the dose of 600 mg in a single administration in combination with Misoprostol as an alternative to uterine aspiration for termination of pregnancy aged less than or equal to 63 days of amenorrhea."

  Protocol No.: FF/92/486/24

This contract includes coverage pursuant to the coverage stipulated by Decree 91.440 of May 14, 1991.

This certification does not signify any presumption of coverage borne by the Insurer.

Paris, July 24, 1992
To be valid for all lawful purposes
FOR THE COMPANY:

[redacted]

ARROWS THIS WAY
ON ORIGINAL

ROUSSEL UCLAF

AMENDMENT NO. 1
TO PROTOCOL FF/92/486/24

"Efficacy and safety of mifepristone (RU 846) administered at the dose of 600 mg in a single administration in combination with Misoprostol as an alternative to uterine aspiration for termination of pregnancies aged less than or equal to 63 days of amenorrhea"

This amendment concerns:

- the withdrawal of the following center:

[ ]

- and its replacement by the following center:

[ ]

We grant formal approval of this amendment.

For the Investigator:

For the Sponsor:

Dr Gu... Valenciennes France 7-1996

LISEZ ATTENTIVEMENT CETTE NOTICE ET FAITES VOUS EXPLIQUER
PAR LE MEDECIN LES POINTS QUI NE VOUS PARAISSENT PAS CLAIRS.

AVANT DE PRENDRE LA MIFEGYNE, LE MEDECIN VOUS FERA SIGNER
- UN FORMULAIRE ATTESTANT QUE VOUS AVEZ LU ET COMPRIS CETTE NOTICE.

INFORMATION DESTINEE AUX PATIENTES

Vous avez demandé une interruption de grossesse. Il vous est proposé de participer à une étude destinée à évaluer, à large échelle, l'efficacité de l'association de Mifégyne et d'une prostaglandine orale, le misoprostol, dans l'interruption volontaire de grossesse.

Cette étude respecte la législation sur les essais clinique et les principes de la déclaration d'Helsinki : elle a été soumise au Comité d'Ethique de l'Hôpital BROUSSAIS qui a rendu un avis favorable le 4 Juin 1991.

Une étude préliminaire a été effectuée chez 100 femmes, et a montré que cette méthode semblait aussi efficace que celle utilisée actuellement, qui associe la Mifégyne à une prostaglandine donnée en injection intramusculaire ou en ovule vaginal. Il est nécessaire de confirmer ces résultats sur une plus vaste échelle et cinq cents femmes participeront à cette étude. Elles seront recrutées dans 24 centres hospitaliers publics ou privés.

La Mifégyne est un médicament qui bloque l'action de la progestérone, hormone du maintien de la grossesse. Son action nécessite toutefois d'être complétée, 36 à 48 heures plus tard, par celle d'une prostaglandine, substance qui augmente les contractions utérines.

L'emploi de la Mifégyne ne peut se faire que dans le respect des règlements en vigueur concernant l'interruption volontaire de grossesse (lois de 1975 et 1979).

Les trois comprimés de Mifégyne doivent être pris moins de 49 jours après le premier jour de vos dernières règles.

La Mifégyne ne doit pas être utilisée dans les cas suivants :

. si la grossesse n'est pas confirmée,

. en cas de suspicion de grossesse extra-utérine,

. si le premier jour de vos dernières règles date de plus de 50 jours,

. si vous êtes âgée de plus de 35 ans,

. en cas d'une des maladies suivantes : insuffisance rénale, insuffisance hépatique, insuffisance surrénale, anomalie de la coagulation sanguine ou prise de médicament anticoagulant, anémie, asthme ou antécédent d'asthme, antécédents cardiovasculaires (angine de poitrine, troubles du rythme, insuffisance cardiaque, hypertension artérielle sévère), diabète, hyperlipémie, glaucome ou pression intraoculaire élevée,

. en cas de traitement prolongé par les corticoïdes,

. si vous êtes fumeuse (au moins 10 cigarettes par jour dans les 2 ans précédents).

L'INTERRUPTION DE LA GROSSESSE PAR LA MIFEGYNE COMPORTE DES LIMITES ET IMPLIQUE DES CONTRAINTES QUE VOUS DEVEZ CONNAITRE

1. La prise de la Mifégyne doit impérativement être suivie 36 à 48 heures plus tard de l'administration d'une prostaglandine, de façon à obtenir l'efficacité maximale de la méthode.

2. La Mifégyne n'est pas efficace à 100 pour cent, et vous ne pourrez pas, par vous-même, juger de l'efficacité de la méthode.
En effet, les saignements utérins qui se produiront ne sont pas une preuve d'efficacité et l'expulsion de l'oeuf, qui survient souvent quelques heures après la prise de prostaglandine, peut être incomplète.

Valenciennes France
17-1/5 96

Laboratoires ROUSSEL
Direction Médicale

Octobre 1991

AMENDEMENT AU PROTOCOLE FFR/91/486/14

(par rapport à la version de Mai 1991)

Efficacité et tolérance de la mifépristone (RU 486) à la dose de 600 mg en prise unique en association au misoprostol comme alternative à l'aspiration utérine dans l'interruption de grossesse d'âge inférieur ou égal à 49 jours d'aménorrhée

NOMBRE DE SUJETS

Page 3, paragraphe 4.1, le nombre prévu de patientes est de 1 000 au lieu de 500.

SUIVI DE L'ETUDE

Après la fin de l'étude des 1 000 sujets prévus, les centres investigateurs qui le souhaitent pourront continuer l'étude. Le suivi d'étude se fera selon le *même protocole*, excepté pour les points suivants :

. le nombre de sujets ne sera pas défini, l'étude s'arrêtera dès que l'A.M.M. sera obtenue pour l'association mifépristone-misoprostol.

. suppression des mesures des taux d'hémoglobine à J1 et J8-J15 (paragraphe 6.2.3, page 7 supprimé).

. un cahier d'observation simplifié sera rempli pour chaque patiente.

DATE : 21 novembre 91

Pour l'investigateur

Pour le promoteur

Dr V. TARGOSZ

Dr R. PEYRON

V. Targosz.

R. Peyron.

EXEMPLAIRE A RETOURNER SIGNE AUX LABORATOIRES ROUSSEL

Laboratoires ROUSSEL
Direction Médicale

Octobre 1991

AMENDEMENT AU PROTOCOLE FFR/91/486/14

(par rapport à la version de Mai 1991)

Efficacité et tolérance de la mifépristone (RU 486) à la dose de 600 mg en prise unique en association au misoprostol comme alternative à l'aspiration utérine dans l'interruption de grossesse d'âge inférieur ou égal à 49 jours d'aménorrhée

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. un cahier d'observation simplifié sera rempli pour chaque patiente.

DATE : Le 21 Novembre

Pour l'investigateur

Pour le promoteur

Dr V. TARGOSZ

Dr R. PEYRON

EXEMPLAIRE A CONSERVER

2 of 2

MIF 004107

Dr Quiquandon
Valenciennes France
7-1/5-96

Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Paris-Cochin

A Paris, le 8 Octobre 1992

27, rue du Faubourg Saint-Jacques
75679 PARIS cedex 14

Réf. du présent avis ou délibération : CC 92 615

Projet de recherche enregistré sous le n° : 92/ 294

Le Comité a été saisi le 1er Septembre 1992

par Mme le Docteur **E. AUBENY**

d'une demande d'avis pour un projet de recherche *N° FF/92/486/24 : "Efficacité et tolérance de la Mifepristone (RU486) administrée à la dose de 600 mg en prise unique en association au Misoprostol en alternative à l'aspiration utérine pour l'interruption de grossesse d'âge inférieur ou égal à 63 jours d'aménorrhée"*,

dont le promoteur est : **ROUSSEL SANTE R ET D**

Le Comité a examiné les informations relatives à ce projet[1], par une deuxième lecture, lors de sa séance du **6 Octobre 1992.**

Ont participé à la délibération :
J. GUERRE, G. OLIVE (1), H. VERNEY (2), G. HAZEBROUCQ, F. LECOURT (3), B. BAILLY (4), E. MORICEAU (5), C. BRIGAUDIOT (7).
(identité et qualité des membres : catégorie).

Le Comité a adopté la délibération suivante : **AVIS FAVORABLE**

Commentaire : **Les modifications demandées à la session du 22/9/92, lors du premier examen, et adressées au CCPPRB le 28/9/92, ont été prises en compte. Aucun commentaire le 6/10/92.**

Signé : Le Président

Cet avis favorable ne vaut que si l'article 209.7 et les articles R. 2047 à R. 2053 sont respectés.

1-2[3]

Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Paris-Cochin

27, rue du Faubourg Saint-Jacques
75679 PARIS cedex 14

A Paris, le 7 novembre 1991

Réf. du présent avis ou délibération : CC 162

Projet de recherche enregistré sous le n° : 91/60

Le comité a été saisi le 31/10/91 par le **Docteur E. AUBENY**

d'une demande d'avis pour amender un projet de recherche intitulé : FFR/91/486/14, "Efficacité et tolérance de la MIFEPRISTONE (RU 486) à la dose de 600 mg en prise unique en association au MISOPROSTOL comme alternative à l'aspiration utérine pour l'interruption de grossesses d'âge inférieur ou égal à 49 jours d'aménorrhée"

dont le promoteur est : **Laboratoires ROUSSEL**

Le comité a examiné les informations relatives à ce projet[1] lors de sa séance du 5/11/91

Ont participé à la délibération : (identité et qualité des membres : catégorie)

F. DOYON, P. POUILLART, (1), H. VERNEY (2), G. HAZEBROUCQ (3), D. VAILLAND (4), M. MORICEAU (5), R. MONGUILLON (6), J.P. LECANUET (7), C. ZARADE (8)

Le comité

a adopté la délibération suivante : **Favorable**
Commentaire éventuel : néant

Signé : Le Président

Cet avis favorable ne vaut que si l'article 209.7 et les articles R. 2047 à R. 2053 sont respectés.

[1] Le comité serait heureux d'être tenu au courant des incidents éventuels ayant pu surgir

COMITE CONSULTATIF DE PROTECTION DES PERSONNES DANS LA RECHERCHE BIOMEDICALE **PARIS-COCHIN (C.C.P.P.R.B.)**

LISTE DES MEMBRES

(Arrêté du 20/5/92; avenant du19/10/1992)

1 - Médecins ou personnes qualifiés en matière de recherche biomédicale :

- DOYON Françoise, Ingénieur d'Etude à l'INSERM
- ASSELAIN Bernard, Biostatisticien - INSERM
- POUILLART Pierre, PU-PH Oncologie Médicale
- WEBER Simon, PU-PH Cardiologie - INSERM
- GENDREL Dominique, PU-PH Pédiatrie
- GUERRE Jean, PU-PH Gastro-entérologue
- HOUSSIN Didier, PU-PH Chirurgie
- OLIVE Georges, PU-PH Pharmacologie

2 - Médecins généralistes :

- SAUREL Patrice
- VERNEY Henri

3 - Pharmaciens :

- HAZEBROUCQ Georges
- ARNAUD Philippe
- LECOURT-GAUTHRON Françoise
- GUERIN Corinne

4 - Infirmières ou infirmiers :

- VAILLAND Danielle
- BAILLY Bernard

5 - Personnes qualifiées en matière d'éthique :

- MORICEAU François
- MOTTAIS Marie-Jo

6 - Personnes qualifiées dans le domaine social :

- ALASSIMONE Huguette
- DALLE Simone

7 - Personnes autorisées à faire usage de titre de psychologue :

- BRIGAUDIOT Chantal
- LECANUET Jean-Pierre

8 - Personnes qualifiées en matière juridique :

- ZARADE Chantal
- GUILLAUME-HOFFNUNG Michèle

IL APPARTIENT A L'INVESTIGATEUR D'AVISER LE PROMOTEUR DE LA REPONSE DU CCPPRB

Valenciennes, France
7-1/5 96

Je tiendrai à la disposition de Roussel Uclaf. et de elle, toutes les données et informations qui concernent directement l'étude.

Je conserverai les données brutes recueillies à l'occasion de cette étude pendant une période de 15 ans.

Nom du produit : Mifépristone
N° de protocole : FF/92/486/24

Date 3 dec 92

Signature de l'Investigateur

[signature]

Date 19/11/92

Signature des Coordinateurs de Roussel Uclaf.

[signature]

PROTOCOLE FF/92/486/24
PERSONNEL DE L'ETUDE

- Dr VAN-GEEM - Docteur
- [redacted] - Docteur
- [redacted] - Infirmière
- [redacted] - Infirmière
- [redacted] - Aide-soignante

PROTOCOLE FFR/91/486/1H

PERSONNEL DE L'ETUDE

- Dr VAN GEEM - Médecin
- Dr [redacted] - Médecin
- [redacted] ICX - Infirmière
- [redacted] Infirmière
- [redacted] - Aide-soignante

EXEMPLAIRE A RETOURNER AUX LABORATOIRES ROUSSEL

19. ENGAGEMENT ET RESPONSABILITE DE L'INVESTIGATEUR

Toutes les informations relatives au produit expérimenté ainsi que les résultats de l'étude sont considérés comme confidentiels.

J'ai lu le protocole et je considère qu'il contient toutes les informations nécessaires à la conduite de l'essai.

Je m'engage à conduire cet essai dans le respect de ce protocole, je n'y apporterai aucune modification sans l'accord écrit des Laboratoires Roussel.

Je m'engage à ne pas débuter l'étude avant qu'un Comité d'Ethique n'ait donné son accord.

Je réaliserai cet essai selon les principes énoncés dans la Déclaration d'Helsinki, et en conformité avec les Bonnes Pratiques Cliniques ; en particulier, j'obtiendrai le consentement éclairé écrit de chaque patiente avant leur entrée dans l'étude.

D'autre part, je m'engage également à rédiger soigneusement les cahiers d'observation, à respecter la procédure en cas d'effet secondaire grave et à contrôler la gestion du produit en expérimentation.

J'accepte le suivi de l'étude par un membre des Laboratoires Roussel ainsi que l'éventualité d'un audit d'assurance de qualité.

Je tiendrai à la disposition des Laboratoires Roussel et des Autorités de Tutelle toutes les données et informations qui concernent directement l'étude.

Je conserverai les données brutes recueillies à l'occasion de cette étude pendant une période de 10 ans.

Nom du produit : MIFEPRISTONE
N° de protocole : FFR/91/486/14

Date 27 juin 91

Signature de l'Investigateur

Date 10/6/91

Signature des Coordinateurs des Laboratoires Roussel

ENGAGEMENT ET RESPONSABILITE DE L'INVESTIGATEUR

Toutes les informations relatives au produit expérimenté ainsi que les résultats de l'étude sont considérés comme confidentiels.

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Je tiendrai à la disposition des Laboratoires Roussel et des Autorités de Tutelle toutes les données et informations qui concernent directement l'étude.

Je conserverai les données brutes recueillies à l'occasion de cette étude pendant une période de 10 ans.

Nom du produit : MIFEPRISTONE
N° de protocole : FFR/91/486/14 (Extension)

Date le 31 dec 91 — Signature de l'Investigateur

Date — Signature des Coordinateurs des Laboratoires Roussel

EXEMPLAIRE A RETOURNER AUX LABORATOIRES ROUSSEL

ENGAGEMENT ET RESPONSABILITE DE L'INVESTIGATEUR

Toutes les informations relatives au produit expérimenté ainsi que les résultats de l'étude sont considérés comme confidentiels.

J'ai lu le protocole et je considère qu'il contient toutes les informations nécessaires à la conduite de l'essai.

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Je tiendrai à la disposition des Laboratoires Roussel et des Autorités de Tutelle toutes les données et informations qui concernent directement l'étude.

Je conserverai les données brutes recueillies à l'occasion de cette étude pendant une période de 10 ans.

Nom du produit : MIFEPRISTONE
N° de protocole : FFR/91/486/14 (Extension)

Date — Signature de l'Investigateur

Date — Signature des Coordinateurs des Laboratoires Roussel

EXEMPLAIRE A CONSERVER

06

Valenciennes France
7-1/5 92

ROUSSEL

ORDONNANCEMENT
Bonnes Pratiques Cliniques
- N° 193/92

Paris, le 18 novembre 1992

Madame le Docteur VAN GEMM
Centre Hospitalier
Service d'Orthogénie
Avenue Desoudrouin

59300 - VALENCIENNES

Madame,

Suite à notre récente conversation téléphonique je vous confirme que l'audit, dans le cadre de votre participation à l'étude Mifépristone misoprostol (FFR/91/486/14) aura lieu le :

Jeudi 10 décembre 1992

à 9h30

et je vous prie de bien vouloir trouver ci-joint la liste des dossiers concernés.

Restant à votre entière disposition pour toute information complémentaire quant au déroulement de cet audit, je vous prie de croire, Madame, en ma considération distinguée.

Responsable Département BPC

1 of 3

FFR/91/486/14

LISTE DES DOSSIERS SELECTIONNES POUR L'AUDIT

CENTRE DE VALENCIENNES

N° patient dans l'étude	Nom (3 premières lettres)	Prénom	Date D'inclusion
602			
619			
620			
624			
626			
752			
759			
760			
776			
1026			
1027			
1036			
1043			
1049			
1448			
1452			
1455			
1460			
1461			
1462			

LIST OF INVESTIGATORS

MIFEPRISTONE-MISOPROSTOL PROTOCOL - No. FFR/91/486/14

Dr AUBENY Elisabeth	BROUSSAIS Hospital-Orthogenics Center	96, rue Didot	75014 PARIS (coordinator) 4	3 95 95 95
Dr BOGHOSSIAN	Henri DUFFAIT Hospital - Sce. OB/GYN Tour Mere-Enfant	305, rue Raoul Follereau	84000 AVIGNON	90 80 33 33
Dr CHAMPION	Hospital de la Conception - Orthogenics Center	147, bd Baille	13006 MARSEILLE Cedex	91 38 37 40
Dr CHARLES Francois	Sce. Obstetrics de l'Quest	Route de Marseille	83190 OLLIOULLES	94 27 91 50
Dr DEQUIDT - Dr. RETTEL	Hospital N.D. de Bon Secours - Sce Gyne.	1, pl. de Vigneulles B.P. 1065	57038 METZ Cedex	94 88 94 48 87 55 34 31
Dr. RENAUD - Dr. FAVREAU	C.H.R.U. Hospital Central	1, place de l'Hopital	67091 STRASBOURG	88.16 17 18
Dr FOURNIE Phillpe	Polyclinique Saint Jean	Avenue de Corbeil	77007 MELUN	64 38 92 00
Dr. FRYDMAN / Dr. HASSOUN-BRUNERIE	Hopital Antonie Beclere - Sce. Gyneco-Obstetrique	157, rue de la Porte de Trivaux	92140 CLAMART	45 37 44 44
Dr LANDEAU Marie Chantal	Hopital BICHAT - Centre d'I.V.G.	46, rue H. Huchard	75018 PARIS	40 25 80 80 (p.54665)
	Clinique Sainte Therese	9, rue Gustave Dore	75017 PARIS	47 63 79 76
Dr LEVADE PUTOIS	Clinique des Teinturiers	1, rue des Teinturiers	31000 TOULOUSE	61 77 33 33
Dr MARIA Bernard	C.H. Intercommunal - Sce. Gynce-Obst.	40, allee de la Source	94190 VILLENEUVE ST. GEORGES	43 86 20 00
Dr. MILLIEZ	C.H. Intercommunal - Sce. Gynce-Obst.	36-40, avenue de Verdum	94010 CRETEIL Cedex	48 98 77 26
Dr. MISSEY KOLB Heliane	C.H. - Orthogenics Center	4, rue Baronne Gerard	78104 ST GERMAN en LAYE	39 73 92 01
Dr. NENY	Hopital BRETONNEAU - Centre d'Orthogenie	2, bd Tonelle	37044 TOURS Cedex	49 47 47 47
Dr. PIDOUX	C.H.G. - Sce Gynco-Obstetrique	Rue de Kersaint Gilly B.P. 237	29205 MORLAIX	98 62 61 60
Dr. PLATEAUX	Hopital BICETRE - Centre d'orthogenie	78, rue General Leclerc	94275 Kremlin Bicetre Cedex	45 21 27 28

082

LIST OF INVESTIGATORS continued

Dr. GEFFROY (mme le)	C.H.G. - Centre d'I.V.G.		44606 St. NAZAIRE	40 90 60 60
Dr. SCHARFMAN	Hopital de la Fraternite	20, ave Julien Lagache B.P. 359	59056 ROUBAIX Cedex	20 99 32 30 (cabinet) 20 54 31 33
Dr. SERFATY - Dr. DREYFUS	Hopital Saint Louis - Centre d'Orthogenie	2, pl de Dr. A. Fournier	75010 PARIS	42 49 49 49
Dr. VAN DEN BOSSCHE Dr. JOURDAN	Hopital Jean DUCOING - Centre d'Orthogenie	15, rue de Varsovie	31000 TOULOUSE	61 77 34 00
Dr VAN GEEN Claudine	C.H. - Service d'Orthogenie	Avenue Desoudrouin	593900 VALENCIENNES	27 14 34 23 27 29 71 73
Dr VIGE	C.H. - Service de Gynco-Ostetrique	3, place Silly	92211 SAINT CLOUD	49 11 60 60 (secret) 49 11 60 17
Dr VITANI	HOTEL DIEU Hopital de la Croix Rousse-Centre d'Orthogenie	1, place de l'Hopital 93, Gde rue de la Croix Rousse	69002 LYON 69317 LYON CEDEX	78 92 20 00 78 29 87 33
Dr. WANG	Clinique de Montrouge	24, rue Perrier	92120 MONTROUGE	46 57 12 45 (cabiner) 45 86 79 00

INVESTIGATORS:

Dr. E. AUBENY
Hopital Broussais
Centre d'Orthogenie
96, rue Didot
75014 PARIS
Tel: (1) 43 95 95 95

Dr. BOGHOSSIAN
Hopital henri Duffaut
Service de gynécologie/obstetrique
Tour Mere-Enfant
305, rue Raoul Follereau
84000 AVIGNON
Tel: 90 80 33 33

Dr. JOURDAN - Dr. VANDENBOSSCHE
Hopital Joseph Ducuing
Centre d'Orthogénie
15, rue de Varsovie
31000 TOULOUSE
Tel: 61 77 34 00

Dr. MISSEY KOLB
C.H. Centre d'Orthogénie
4, rue Baronne Gérard
78104 ST GERMAIN EN LAYE
Tel: 39 73 92 01

Dr. NENY
Hopital Bretonneau
Centre d'Orthogénie
2, bd. Tonellé
37044 TOURS
Tel: 47 47 47 47

Dr.MARIA
Centre Hospitalier
Intercommunal
Sce de Gynéco/Obstétrique
40 Allée de la Source
92195 Villeneuve St. Georges
Tel: 43 86 20 00

Dr. RETTEL
Hopital N.D. de Bon Secours
Service de gynécologie
1, pl. de Vigneulles
B.P. 1065
57038 METZ CEDEX
Tel: 87 55 31 31

Dr. SCHARFMAN
Hopital de la Fraternité
20, avenue Julien Lagache
B.P. 359
59065 ROUBAIX CEDEX
Tel: 20 99 32 30
20 54 31 33 (cabinet)

Dr. VAN GEEM
C.H. Service d'Orthogénie
Avenue Désandrouins
59300 VALENCIENNES
Tel: 27 14 34 23
27 29 71 73

Dr. VITANI
Hopital de la Croix Rousse
Centre d'Orthogénie
93, Gde rue de la Croix Rousse
69317 LYON CEDEX
Tel: 78 29 87 33

Dr. WANG
Clinique de Montrouge
24, rue Perrier
92120 MONTROUGE
Tel: 46 57 12 45
45 86 79 00 (cabinet)

MONITORING VISITS ASSESSMENT LIST

24

Drug : **Study :**

Investigator : **Location :**

Monitor :

Date of monitoring visit	Signature of investigator attesting monitoring visit	Signature of monitor attesting monitoring visit
23 02 93		
25 04 [illegible]		

Appendix A.1, Table 15
Roussel Protocol FF/92/486/24

Follow-Up Visit Day 10-18
Uterine Bleeding

Center: Dr. Van Geem

Patient Number	Uterine Bleeding: Any Bleeding	Uterine Bleeding: Start Date	Uterine Bleeding: Duration (Days)	Did Uterine Bleeding Require ?: Hemoglobin Test? [1]	Test Date	Value (g/dl)	Tranfusion	Packed Red Cells	Medical Treatment? [2]	Surgery For Bleeding?
751	Yes			Yes	02/22/93	5.9	Yes	3	No	No

(Continued)

* Misoprostol not administered.
** Second dose of Misoprostol not administered.
[1] Sooner than that of normal follow-up visit.
[2] Medical treatments listed in Appendix A.1, Table 17.

APPEARS THIS WAY
ON ORIGINAL

f:\po\french\mif24\saspgms\apdxa1\bleed696.sas 20JUN96:09:19

Dr Quinquenel
Valenciennes, France
7-1/5 96

MIF 004124

Appendix A.1, Table 11
Roussel Protocol FF/92/486/24

Adverse Events Which Required Hospitalization
Except for Nausea, Vomiting, Diarrhea and Painful Uterine Contractions
Between Mifepristone and Misoprostol Administration, Within 3 Hours After First Misoprostol Administration
or Within 2 Hours After Second Misoprostol Administration

Center: Dr. Van Geem

Pt #	Symptom	Start Date	Start Time	Stop Date	Stop Time	Severity	Related To MIF [1]	Related To MIS [1]	Action Required	Specify	Outcome
63	Metrorrhagia	12/10/92		12/17/92		Moderate	4	4	Yes	Hospitalization + Other: Aspiration	Complete recovery
751	Gastritis	02/09/93	13:00	02/09/93	20:00	Moderate	2	0	No		Complete recovery
	Metrorrhagia			02/24/93		Moderate	4	4	Yes	Hospitalization	Complete recovery
	Anemia			02/24/93		Severe	3	3	Yes	Medical treatment (Transf)	Complete recovery
980**	Headache	03/23/93	20:00	03/25/93	8:00	Mild	2	0	No		Complete recovery
	Metrorrhagia	03/25/93	20:00			Moderate	4	4	Yes	Treatment + Hospitalization + Other: Curettage	Complete recovery
	Anemia			Ongoing		Moderate	4	4	Yes	Medical treatment	Treatment in progress

(Continued)

* Misoprostol not administered.
** Second dose of Misoprostol not administered.
[1] 0=not related, 1=doubtful, 2=possible, 3=probable, 4=very probable.

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ON ORIGINAL

f:\pc\french\mif24\saspgms\apdxa1\ade696.sas 20JUN96:16:19

FILE ASSIGNED: 9/96 PRIORITY: 2 DATE INSP 6-24/28-96 GRP
CENTRAL FILE NO. JD/TA. CNTY PHONE

EMPL NO. 101

NAME: Dr. Elisabeth Aubeny STREET: Broussais Hospital, 97 rue Didot

CITY: 75014 Paris STATE: France ZIP. DISTRICT:

ENDORSEMENT

The Population Council, New York, has filed NDA-20687, Roussel's abortion pill RU-486 which relies in part on studies conducted by Dr. Aubeny.

Both studies 14 and 24 were covered. There was a failure to maintain complete and accurate study records, with lab reports missing, lab reports mis-dated, lab reports with falsified dates, missing ultrasound reports, and unreported aspirations. Study 14 had four inelligible subjects. Some consent forms were dated after the start of the studies, and the investigator has signed as having "witnessed" the subject's signing the consent form up to four days prior to the subject's signing. There were also under-reported side effects, such as bleeding with two subsequent aspirations, convulsions reported only as fainting, expulsion that was actually a surgical evacuation.

APPEARS THIS WAY
ON ORIGINAL

VOLUNTARY CORRECTION DATA

PAC	PROBLEM TYPE	CORRECTIVE ACTION	EST COST OF ACTION	DATE ACTION VERIFIED	CORRECTING UNIT	REPORTING DISTRICT

SIGNATURE /S/ DATE 11/12/96
Supervisory Investigator

DISTRIBUTION
DAL-DO - O w/ O Exhibits Then to HFD-133
HFD-344 - CC w/Original Exhibits
FTS-RP - CC w/o Exhibits
CHRON, LCAN, BIMO Monitor - E/S

FORM FDA 481(E)-CG (10/91)

6 / 96 PRIORITY 2 DATE INSP 6-24/28-96 GRP

CENTRAL FILE NO JD/TA CNTY PHONE

NAME Dr. Elisabeth Bubeny STREET Broussais Hospital, 97 rue Didot

CITY 75014 Paris STATE France ZIP DISTRICT

RELATED FIRMS. none ST-ASSGN. ITS

REGISTRATION.

REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR
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ESTABLISHMENT TYPES/ 1: 2: 3:
INDUSTRY CODES ON OEI

TOTAL ESTAB. SIZE	I.S. BUSINESS RECEIVED	SOLD	DISTRICT USE #1	#2	#3	RECALL NO.	REFUSAL CODE	PROFIL	PASS FAIL
1	YES NO	Ø	*			Ø	Ø		

ESTAB-CHANGES NEW-FIRM NONE NAME ADDRESS OWNERSHIP SIZE PROD CODE
OTHER EST-TYPE O/B INACTIVE NOT OEI AUX-FIRM REGISTRATION

PAC	PROCESS (PRODUCT) CODE	EST TYPE	INSP BASIS	EMPL1 PC NO. HD	EMPL2 PC NO. HD	EMPL3 PC NO. HD	PRODUCT	PRIORITY	RESCHED DATE	INSP CONC	DIST DCSN
48R806	61Z	7	2	—			Protocols 9114 and ~~9224~~	—		A	E

SAMPLES COLLECTED:
SAMPLE # Ø PRODUCT Ø

HEADQUARTERS UNIT REFERRED: HFC-134, HFD-344 FD 483 ISSUED YES NO

REASON REFERRED routine OTHER FED GOVT INSP. OR GRADING

INSPECTOR'S NAME/SIGNATURE: /S/ SUPERVISOR'S NAME/SIGNATURE

HFD-344 FORM FDA 481(A)-CG (09/04)

/S/

PRODUCTS COVERED

EMPL NO. 101

ABLI HMENT NAME Dr. Elisabeth Aubeny

E IT SPECTED. 6-24/28-96 DATE ASSIGNED. 6/ 96

E ERED	PRODUCT CODE	EST TYP	EST TYP	EST TYP	PRODUCT DESCRIPTION
24/96	61Z	7			Protocols 9114 and 9224, Roussel's RU-486
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FORM FDA 481(C)-CG (10/80)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

1/22/97

Elizabeth Aubeny,M.D.
Broussais Hospital
97 rue Didot
75014, Paris, France

Dear Dr. Aubeny:

On June 26,1996, [redacted] and [redacted] representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of two clinical studies (protocol #FFR/91/486/14 and #FF/92/486/24) of the investigational drug Mifepristone, performed for Roussel laboratories and submitted by the Population Council in support of their New Drug Application. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you did not adhere to all good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. At the close of the audit , you were presented a form FDA 483 which listed the inspectional observations including failure to maintain accurate and complete study records(i.e., supporting laboratory records could not be located for some of the subjects), inclusion of four ineligible subjects into the clinical trials, and the under reporting of adverse events to the study sponsor.

We appreciate the cooperation shown [redacted] and [redacted] during the inspection.

Sincerely yours,

/S/

[redacted]

Clinical Investigations Branch
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

bcc:
HFA-224
HFD-344
HFD-340 r/f
HFD-342
HFD-580 Review Division Div. ——— Doc. Rm.: NDA#20-687
——————— CSO
HFC-230
HFC-132

r/d: ——— :1/14/97
finaled: —— 1/14/97

CFN:
Field classification:NAI
Headquarters classification:
_____1)NAI
__X__2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is different classification, explain why:

Deficiencies noted:
_____ inadequate consent form
_____ inadequate drug accountability
_____ failure to adhere to protocol
__X__ inadequate records
__X__ failure to report ADRS _____
_____ other (specify)

M.O. notes:

APPEARS THIS WAY
ON ORIGINAL

DATE ASSIGNED: PRIORITY: 2 DATE INSP: [illegible] GRP:
CENTRAL FILE NO.: 9614338 JD/TA: CNTY: PHONE:
EMPL NO: 101
NAME: Dr. Elisabeth Aubeny STREET: Broussais Hospital, 97 rue Didot
CITY: 75014 Paris STATE: France ZIP: DISTRICT:

ENDORSEMENT

The Population Council, New York, has filed NDA-20687, Roussel's abortion pill RU-486 which relies in part on studies conducted by Dr. Aubeny.

Both studies 14 and 24 were covered. There was a failure to maintain complete and accurate study records, with lab reports missing, lab reports mis-dated, lab reports with falsified dates, missing ultrasound reports, and unreported aspirations. Study 14 had four inelligible subjects. Some consent forms were dated after the start of the studies, and the investigator has signed as having "witnessed" the subject's signing the consent form up to four days prior to the subject's signing. There were also under-reported side effects, such as bleeding with two subsequent aspirations, convulsions reported only as fainting, expulsion that was actually a surgical evacuation.

cancel — S — HFC-134
151
NOV 25 1996

VOLUNTARY CORRECTION DATA

PAC	PROBLEM TYPE	CORRECTIVE ACTION	EST. COST OF ACTION	DATE ACTION VERIFIED	CORRECTING UNIT	REPORTING DISTRICT

SIGNATURE /S/
Supervisory Investigator

DATE: 11/12/96

DISTRIBUTION:
DAL-DO - O w/o Exhibits then HFC-133
HFD-344 - CC w/Original Exhibits
FTS-RP - CC w/o Exhibits
CHRON, LCAW, BIMO Monitor - C/S

FORM FDA 481(E)-CG (10/81)

961433S

DATE ASSIGNED: 6 / 96 PRIORITY: 2 DATE INSP:6-24/28-96 GRP:

CENTRAL FILE NO..961433S JD/TA. CNTY: PHONE.
NAME: Dr. Elisabeth Aubeny STREET:Broussais Hospital, 97 rue Didot
CITY: 75014 Paris STATE:France ZIP: DISTRICT:

RELATED FIRMS: none ST-ASSGN: ITS:

REGISTRATION:

REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR
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ESTABLISHMENT TYPES/ 1:__ 2:__ 3:__
INDUSTRY CODES ON OEI: __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

TOTAL ESTAB. SIZE	I.S. BUSINESS RECEIVED	SOLD	DISTRICT USE #1	#2	#3	RECALL NO.	REFUSAL CODE	PROFIL	PASS FAIL
1	YES NO	Ø %				Ø	Ø		

ESTAB-CHANGES: NEW-FIRM NONE NAME ADDRESS OWNERSHIP SIZE PROD CODE
OTHER: EST-TYPE O/B INACTIVE NOT OEI AUX-FIRM REGISTRATION

PAC	PROCESS (PRODUCT) CODE	EST TYPE	INSP BASIS	EMPL1 PC: NO: HD	EMPL2 PC: NO: HD	EMPL3 PC: NO: HD:	PRODUCT	PR IT Y	RESC HED DATE	INSP CONC	DIST DCSN
48R806	61Z	7	2	—			Protocols 9114 and 9224		—	A	E

SAMPLES COLLECTED:
SAMPLE# Ø PRODUCT: Ø

cancel: ~~1S~~ ~~HFC-134~~ 1S

NOV 25 1996

HEADQUARTERS UNIT REFERRED: HFC-134, HFD-344 FD 483 ISSUED: YES NO

REASON REFERRED routine OTHER FED GOVT INSP.OR GRADING:

INSPECTOR'S NAME/SIGNATURE: SUPERVISOR'S NAME/SIGNATURE: /S/

HFD-344 FORM FDA 481(A)-CG (09/84)

/S/

MIF 004132

PRODUCTS COVERED

CFN: 9614338 EMPL NO.: 101

ESTABLISHMENT NAME: Dr. Elisabeth Aubeny

DATE INSPECTED: 6-24/28-96 DATE ASSIGNED: 6/96

DATE COVERED	PRODUCT CODE	EST TYP	EST TYP	EST TYP	PRODUCT DESCRIPTION
6/24/96	61Z	7			Protocols 9114 and 9224, Roussel's RU-486
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FORM FDA 481(C)-CG (10/80)

MIF 004133

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Dr; Elisabeth Aubeny	PERIOD OF INSP: é(2[illegible] to 28 June 1996	C. F. NUMBER
TITLE OF INDIVIDUAL Clinical Investigator	TYPE ESTABLISHMENT INSPECTED Clinical Investigator	
FIRM NAME BROUSSAIS Hospital	NAME OF FIRM, BRANCH OR UNIT INSPECTED same	
STREET ADDRESS 97, rue Didot	STREET ADDRESS OF PREMISES INSPECTED	
CITY AND STATE (Zip Code) 75014 PARIS France	CITY AND STATE (Zip Code)	

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

*1; FAILURE TO MAINTAIN COMPLETE AND ACCURATE STUDY RECORDS/

a; Laboratory reports are missing for 8 of 44 subjects in study 14 and 3 of 52 for study 24:

b. Wrong dates on lab reports or wrong date reported for 11 of 44 subjects for study 14 and 1 of 52 for study 24.

c. One Lab report for each study has had the date changed from another existing lab report; to make them appear to be separate new reports as subject 9 in study 24 and 745 in study 14. 151

d. Reported ultrasound documents are missing for 13 of 44 subjects for study 14 and 7 of 52 for study 24.

e. Page 5 of case report 26 for study 14 is missing; pages 14, 15, 16 of the case report forms are missing from some study 24 files.

f. Unreported aspiration (799 of study 24* or no aspiration clinic docu,entation (472 of study 24*.

2. Four inelligible subjects were entered into study 14 [redacted] (4, 5, 1377, 1638)

3. Consent forms dated after the start of study (2 of 44 for study 14 ane 1 of 52 for study 24, and investigator has signed consent form sometimes in advance up to 4 days of subjects signing.

4. Under-reported side effects; as for example 793 of study 24 (bleeding with two subseauent aspirqtions); 748 (reported "convulsions" as "fainting") 26 of study 24 ("expulsion" was qctually a surgical "evacuation"); 5 of study 14 (bleeding), 648 (nausea and contrations), or *[redacted] (bleeding and pelvic pain); ~~725~~ 1275 151

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE /S/	EMPLOYEE(S) NAME AND TITLE (Print or Type) Investigator	DATE ISSUED 28 June 96

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE OF PAGES

EIR

Dr. Elisabeth Aubeny
Broussais Hospital
97, rue Didot
75014 Paris, France

Inspection Dates: June 26-28, 1996

Investigator: [redacted]

SUMMARY OF FINDINGS

The French drug firm, Roussel, has had the abortion pill RU-486 (Mifepristone) on the European market for some years. The Population Council of New York City has NDA 20-687 pending, which relies in part on the two studies, 9114 and 9224, begun in France in 1991 and 1992. These studies were reviewed during this inspection.

Review of the study records revealed a failure to maintain complete and accurate records; e.g., laboratory reports that were missing for 8 of 44 subjects in Study 14, and 3 of 52 subjects for Study 24. Wrong dates were on lab reports or wrong dates reported for 11 of 44 subjects for Study 14. One lab report for each study had the date changed from another existing lab report to make them appear to be separate new reports; missing ultrasound documents for 13 of 44 subjects for Study 14, and 7 of 52 for Study 24; pages missing from the case record files and unreported aspirations; four ineligible subjects who were entered into Study 14; consent forms were dated after the start of study for some subjects, and the investigator had signed consent form sometimes in advance, up to 4 days before the subjects had signed.

Other problems included under-reported side effects; e.g., a patient bleeding with two subsequent aspirations; convulsions reported as fainting; and expulsion which was actually a surgical evacuation; bleeding, nausea and contractions, or bleeding and pelvic pain.

Nevertheless, CDER's (HFD-344) [redacted] assured the clinical investigator that he would not recommend that the studies not be used in support of the NDA application.

PURPOSE OF INSPECTION

The Population Council has NDA 20-687 pending for Roussel's Mifepristone as an abortion pill. In support of ~~that~~ application, two studies were to be audited during this inspection, No. 9114 and No. 9224 (here in after referred to as No. 14 and 24, respectively.) They were begun in 1991 and 1992 in France. The firm inspected, Dr. Elisabeth Aubeny, was selected because of the relatively large number of patients included in these two studies.

FIRM'S FACILITIES

This is a French government-supported abortion clinic. The firm is not equipped to do surgery, and if such is required, it must be done at other facilities. Under French rule, two doctor

opinions are necessary. The first is for referral, and the second used for the abortion doctor, in this case, Dr. Elisabeth Aubeny.

PERSONS INTERVIEWED

The following individuals were present at one time or another during this inspection:

Dr. Elisabeth Aubeny, Principal Clinical Investigator

Ann Robbins, Ph.D.; Staff Scientist
Contraceptive Development Program
Center for Biomedical Research
The Population Council
1230 York Avenue
New York, NY 10021

[redacted]

[redacted] member of the French FDA, was present to make sure that the privacy laws were met.

[redacted]

[redacted] acted as interpreter, as neither [redacted] nor I are fluent in French.

[redacted]

"Continued"

[redacted] was also there to help assure that confidentiality was maintained.

[redacted] was present on June 27 when [redacted] had other business to attend and was not present.

STUDY DESIGN

Both of these studies are basically the same, the only difference is that Study 14 is for patients with an amenorrhea of 49 days or less who want to have an abortion. Study 24 extends the amenorrhea age up to 63 days.

The women had to be referred from their own doctor to the abortion doctor, and French law requires that these abortions be voluntary--that the patient must ask for an abortion.

Once legal niceties have been met, the patient is given three oral tablets, 200 mg Mifepristone each, and then instructed to come back in 48 hours on Day 3. If there has been no expulsion of the embryo and embryonic materials, the patient is given two 0.2 mg Misoprostol tablets, which is a prostiglandin to evacuate the uterus. The patients were to remain in the clinic for a 4-hour observation period following the prostiglandin administration, and then given an appointment to come back in 1-2 weeks for a final assessment. That assessment was rated as either "complete expulsion," "incomplete expulsion," "ongoing pregnancy," or "surgical procedure for bleeding." Complete expulsion was classed as "treatment success," where all the other conditions were considered to be treatment failures.

Study 14 was conducted in 1991 and 1992, and Study 24 was conducted primarily in 1993. As stated, both studies were essentially identical, the only difference being that Study 14 was for gestational age of 49 days, and Study 24 extended the gestational age to 63 days.

AUTHORITY AND ADMINISTRATION

Roussel personnel explained to the clinical investigator the nature of the protocol and the obligations of conducting a clinical investigation, and appropriate documents are submitted as exhibits with this report.

Also included as exhibits with this report is the list of people who were authorized under Dr. Aubeny to administer the test articles. Both studies continued to completion, with no discontinuation of either study.

This is an abortion clinic. All patients coming here are referred from outside doctors; i.e., most likely the patient's own personal physician. As such, there were laboratory reports, ultrasound reports and things of that nature that came from outside facilities, as chosen by the patient prior to coming to Dr. Aubeny. Examples of such are included as exhibits with this report.

PROTOCOL

Attached as exhibits with this report are copies of protocols used for each of the studies audited during this inspection. There were no amendments or changes, and the protocols remained unchanged regarding the subject selection, number of subjects, frequency of subject observations, dosage, route of administration, and frequency of dosage. Both protocols were approved by the appropriate Institutional Review Board (IRB).

SUBJECT RECORDS

Dr. Aubeny had the files of case record form booklets for each patient in each study. In addition, there were patient charts for each subject in the study, and these consisted of such things as various laboratory or ultrasound reports that had been furnished with the referral letter prior to the patients coming to the clinic. There were also records of dosing and subsequent expulsion or adverse event, or other observations. All records were in French.

None of the patients were contacted, but there was adequate documentation to assure they were real individuals.

The Population Council has submitted for both studies certain printouts by subject number, and that information was compared with the information in the clinical investigator's patient files. We did not review files for all subjects, but we did for 44 subjects for Study 14, and 52 subjects for Study 24. There were 210 subjects enrolled in Study 14. The first patient was enrolled in Study 14 on 6/27/91 and the last on 9/10/92. For Study 24, 219 subjects were entered. There were entries in the records for patient dosage, results, and general observations, including adverse events.

As for completeness and accuracy of the study records, see the subsequent heading in this report FDA-483 Observations and Management Response which identify such problem areas.

OTHER STUDY RECORDS

A total of 210 subjects were entered in Study 14, and 219 for Study 24. The NDA applicant is not the sponsor firm in this case, and the application is made by the Population Council on Roussel's drug, Mifepristone (pending NDA 20-687). I discussed with Dr. Robbins the procedures that were used to generate the printout supplied to FDA Headquarters by the Population Council, and she roughed out a chart for me which I have included as an exhibit. The exhibit is a listing of the source documents, the location, and what action was taken, such as audits by the Population Council and their hired firm [redacted] The source documents and the French CFR's are in the clinic files.

Roussel Headquarters in France has the original case record files, and these have been transferred to an electronic data base and given to the Population Council, which was the basis for the NDA data files by the Population Council. [redacted] is the one who was instrumental in transferring the information from the source documents and the French case record forms (CRF) to the computer printout, which are in the custody of the Population Council.

INFORMED CONSENT

Included as Exhibit 27 is a copy of the informed consent that was actually used. There is also an English language translation of this document.

Consent forms were sometimes dated after the start of the study (two for Study 14, and one for Study 24). The investigator had sometimes signed a consent form as having witnessed the signature of the subject in advance, up to 4 days before the subject had signed. See subsequent heading FDA-483 Observations and Management Response.

Included as exhibits are copies of the information provided to the patients seeking abortion.

INSTITUTIONAL OR OTHER REVIEW BOARDS

Both studies received appropriate institutional review board approval, and such documents are included as exhibits.

SPONSOR AND MONITORING

Included as exhibits with this report is a list of monitor names and dates of visits. Monitors collected the original CRF's, and left copies for Dr. Aubeny. In this way, the sponsor firm,

Roussel, was kept apprised on a timely basis of the conduct of the study and any unusual events that might have occurred.

TEST ARTICLE ACCOUNTABILITY

We reviewed drug accountability records for both studies, and in a word, these were complete with no discrepancies noted.

RECORDS RETENTION

Those records in the clinic's possession are maintained forever. I have no information on records maintained at Roussel or by the Population Council.

FDA-483 OBSERVATIONS AND MANAGEMENT RESPONSE

At the conclusion of the inspection an FDA-483 Form, Inspectional Observations, was presented to Dr. Elisabeth Aubeny and discussed with her in the presence of Ann Robbins, Late in the conference, we were joined by whose only concern was confidentiality.

The FDA-483 observations with comments is as follows:

1. Failure to maintain complete and accurate study records:

   a. Laboratory reports are missing for 8 of 44 subjects in Study 14 and 3 of 52 for Study 24.

      COMMENTS: The missing lab reports are for Subjects 1, 6, 10, 13, 726, 734, 750, and 848. The laboratory reports missing for Study 24 are for Subjects 2, 786 (verbal only), 805 (telephone report only).

   b. Wrong dates on lab reports or wrong date reported for 11 of 44 subjects for Study 14, and 1 of 52 for Study 24.

      COMMENTS: Such errors were noted for Study 14 for Subjects 9, 727, 731, 743, 848, 861, 1276, 1271, 1653, and for Study 24, Subject 795.

c. One lab report for each study has had the date changed from another existing lab report to make them appear to be separate new reports, as Subject 5 in Study 24 and Subject 745 in Study 14.

COMMENTS: In the Population Council-supplied printout for Study 14, Subject 744 and 745 are mistakenly misidentified; i.e., the Subject listed as 744 is actually 745 and 745 is actually 744.

Exhibit 1 with this report is a copy of the printout supplied by the Population Council to FDA for Study 14, Subject 745, (erroneously listed as 744 on the printout) which shows for the third item, BETA HCG dated September 30, 1991, with a value of 41870. This is believed to be a made up date with value taken from the actual lab report of July 23, 1989, which is Exhibit 2.

Exhibit 3 is a laboratory report for Subject 3, Study 24, which has 18 crossed out and listed as 3, so that the date reads December 3, 1992. This is exactly the same laboratory report which is Exhibit 4, dated December 18, 1992. Since the firm had no laboratory report for the 3rd, they simply crossed out the 18 date on a copy and wrote 3 as seen in the exhibits. These values then were presented as a legitimate lab report from December 3, 1992, which did not happen.

FIRM'S COMMENTS: Dr. Aubeny appeared to be unaware that this had occurred, having been changed or substituted by some unknown member of her staff, and she was not pleased that such things had occurred. She agreed that it was better to have a missing document, and simply leave the value blank, than to pretend that a document existed by manipulating dates on other documents.

d. Reported ultrasound documents are missing for 13 of 44 subjects for Study 14, and 7 of 52 for Study 24.

COMMENTS: For Study 14, ultrasound documents were missing for Subjects 3, 4, 8, 9, 11, 13, 14, 26, 731, 743, 1275, 1276, and 1634. For Study 24, the missing ultrasounds were for the Subjects 798, 802, 808, 814, 824, 826, and 832.

e. Page 5 of case report 26 for Study 14 is missing; pages 14, 15, 16 of case report forms are missing from some Study 24 files.

COMMENTS: There was no explanation for such missing documents.

f. Unreported aspiration (799 of Study 14) or no aspiration clinic documentation (472 of Study 24).

2. Four ineligible subjects were entered into Study 14 (4, 5, 1377, 1638).

COMMENTS: Subject 4 had an extra uterine pregnancy, which made her ineligible. Subject 5 smoked too many cigarettes (See Exhibit 5). Patient 1377 had a 53-day pregnancy, and 1638 had a 55-day pregnancy, which made them ineligible for Study 14 (although they could have been acceptable for Study 24). Subject 1650 was questionable as far as gestation length, but was not included in these four that we knew for certain were ineligible.

3. Consent forms dated after the start of study (2 of 44 for Study 14, and 1 of 52 for Study 24); and investigator has signed consent form sometimes in advance up to 4 days of subject's signing.

COMMENTS: Exhibit 7 is a handwritten chart of all the patients in Study 24, listing the patient number, first three letters of the name, the date of consent, the first dose date, the second dose date, and ending with the effect whether there was an adverse effect or not. That patient which is 831 (Exhibit 7) shows a "date consentment" of 3/9/93, with the first dose on 3/7/93. Exhibit 10 is a page from Patient 831 inclusion criteria, which was done on 3/5/93, according to the document.

Exhibit 11 is the informed consent, which Dr. Aubeny had signed on 3/5 in advance of the patient having signed on the 9th of March. Likewise, Exhibit 6 is the same kind of handwritten chart for Study 14, listing all the patient numbers, the first three letters of the name, "date consentment" and dose dates, and this shows that for Subjects 726, 1111, 1271, the "date consentment" was 2-days after the first dose was administered. These dates were checked and the chart agrees with the consent dates in the patient files.

FIRM'S COMMENTS: Dr. Aubeny stated that the reason that some of her signatures as witnessing the informed consent signature of the patient were sometimes several days in advance of the patient signing was that the information was read to the patient on a previous day, and the patient was

believed to have verbally agreed to the procedures, and only later actually signed the document.

It was pointed out to Dr. Aubeny that it takes but a few seconds to sign as having witnessed the signature of the patient granting her informed consent,

and this is how that should be done. Dr. Aubeny stated this would be the procedure used in the future.

4. Under-reported side effects; e.g., Subject 793 of Study 24 (bleeding with two subsequent aspirations); 748 (reported "convulsions" as "fainting"); 26 of Study 24 ("expulsion" was actually a surgical "evacuation"); 5 of Study 14 (bleeding), 848 (nausea and contractions), or 1,275 (bleeding and pelvic pain).

   COMMENTS: Pages 511 through 514 of Exhibit 9 are the Population Council-generated printout for the Subject 793 of Study 24 covering adverse effects, and this document lists only one adverse effect, a fever, a temperature in excess of 38°. However, multiple documents that are included as Exhibit 12 for Subjects 793, show that there was bleeding to the extent that two aspirations were necessary.

   Exhibit 15 is a multi-page document of adverse events for Study 24, supplied by Population Council, which shows for Subject 793, that there was one symptom, fever of moderate severity, with complete recovery.

   Exhibit 8 is the Population Council-provided printout for various subjects in Study 14, and pages 53 and 54 cover the Subject 748, and list the single adverse effect as fainting, but the documents for this patient included as Exhibit 16 show not only the patient falling (French "chute" equals English "fall"), but two convulsions. It is our view that fainting is not the same as convulsions. Likewise, we do not believe any event should be listed as an expulsion, which was actually a surgical evacuation.

   FIRM'S COMMENTS: It was indicated that the database could be corrected to show convulsions instead of, or in addition to fainting.

Notwithstanding these objectionable conditions, [redacted] assured Dr. Aubeny that he would not recommend that the studies not be included in the evaluation of the NDA application.

EXHIBITS

Exhibit 1 Printout for Subject 745.

Exhibit 2 Lab report for Subject 745.

Exhibit 3 Lab report for Subject 3 with date falsified.

Exhibit 4 Actual lab report for Subject 3.

Exhibit 5 Documents for Subject 5 showing ineligibility because of heavy cigarette smoking.

Exhibit 6 Multi-page chart for Study 14.

Exhibit 7 Multi-page chart for Study 24.

Exhibit 8 Excerpts from printout for Study 14.

Exhibit 9 Excerpts from printout for Study 24.

Exhibit 10 Inclusion criteria sheet of CRF's for Subject 831.

Exhibit 11 Signed consent for Subject 831.

Exhibit 12 Multiple documents for Subject 793, Study 24.

Exhibit 13 Lab normals.

Exhibit 14 Document flow chart.

Exhibit 15 Study 24, adverse event listing.

Exhibit 16 Documents for Patient 748.

Exhibit 17 Protocol actually used for Study 14.

Exhibit 18 Protocol actually used for Study 24.

Exhibit 19 Monitoring visit list.

Exhibit 20 Treatment record for bleeding and pelvic pain for Subject 1275.

Exhibit 21 Document (2 pages) showing IRB approval, including members present and absent.

Exhibit 22 IRB members (this is a second [redacted] IRB).

Exhibit 23 IRB approval by the [redacted] IRB.

Exhibit 24 Equivalent of Statement of Investigator.

Exhibit 25 Product Insert for Mifepristone by Roussel.

Exhibit 26 Information for patient.

Exhibit 27 English version information for patient, with English version written informed consent.

Exhibit 28 Document outlining delegation of authority for administration, responsibilities for the pharmacy's storing and dispensing the product, as well as archiving documents.

/S/

Ft. Smith Resident Post
Dallas District Office

Clinical Investigations Branch
CDER (HFD-344)

101096:102196

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Clinical Investigator or Sponsor:

Routine ☒ - F/C ☐ Biopharm. ☐ Elizabeth Aubrey

CIB

DATE	TO	ACTION REQUESTED
1/20/96	—	
1/4/97	—	aubrey C.I.T
1/4/97	—	
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Jan 97	—	O/P 2 2 1997

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SNAME	CITY	ST	IN	ASSIGN	RECD DATE	ACTN DATE	CLASS	REVIEWER
AUBENY	PARIS	NG	DA	31-MAY-96	20-NOV-96	22-JAN-97	VAI	—
QUIQUEMPOIS	VALENCIENNES	NG	DA	31-MAY-96	20-NOV-96	22-JAN-97	VAI	—

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With the distributed, parallel query and Parallel Server options
PL/SQL Release 2.1.5.2.0 - Production

DO YOU WANT TO LOOK AT REPORT AGAIN? <Y,N>

NDA
20-687: Mifepristone

E-mail from — 11/6/98
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FORMULAIRE D'INFORMATION DESTINE AUX PATIENTES ET CONSENTEMENT ECLAIRE ECRIT

N° DE PROTOCOLE : FF/92/486/24

TITRE DE L'ETUDE : Efficacité et tolérance de la Mifépristone administrée à la dose de 600 mg en prise unique en association au Misoprostol (en alternative à l'aspiration utérine) pour l'interruption de grossesse d'âge inférieur ou égal à 63 jours d'aménorrhée.

N° DE LA PATIENTE :

Vous avez demandé une interruption de grossesse. Il vous est proposé de participer à une étude destinée à évaluer, à large échelle, l'efficacité de l'association de Mifépristone et d'une prostaglandine orale, le misoprostol, dans l'interruption volontaire de grossesse allant jusqu'à 63 jours d'aménorrhée.

Cette étude respecte la législation sur les essais cliniques et les principes de la déclaration d'Helsinki : elle a été soumise au Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de l'Hôpital Cochin qui a rendu un avis favorable le 6 Octobre 1992.

En mai 1992, le Ministère de la Santé a accepté la mise sur le marché de l'Association Mifépristone 600 mg + 2 comprimés de Misoprostol pour des interruptions volontaires de grossesse allant jusqu'à 49 jours d'aménorrhée. Cette association permet en effet d'obtenir une interruption et une expulsion complète de la grossesse dans 95% des cas.

Une étude anglaise, effectuée chez 957 femmes a montré que l'association de la Mifépristone à une prostaglandine donnée en ovule vaginal conservait cette même efficacité jusqu'à 63 jours d'aménorrhée.

Par ailleurs, une étude préliminaire, faite en France, sur 229 patientes a montré que l'administration d'un 3ème comprimé de Misoprostol (en cas de non expulsion dans les 3 heures qui suivent la prise des 2 premiers comprimés) amenait le taux de succès global à 99%; de plus, avec ce type de schéma thérapeutique, l'expulsion est survenue dans le centre hospitalier, c'est-à-dire avant la fin de la 4ème heure, chez 88,4% des femmes.

Il est nécessaire de confirmer ces 2 observations sur une plus vaste échelle et 1000 femmes participeront à cette étude.

Elles seront recrutées dans 11 Centres Hospitaliers privés ou publics.

La Mifépristone est un médicament qui bloque l'action de la progestérone, hormone du maintien de la grossesse. Son action nécessite toutefois d'être complétée, 36 à 48 heures plus tard, par celle d'une prostaglandine, substance qui augmente les contractions utérines.

L'emploi de la Mifépristone ne peut se faire que dans le respect des règlements en vigueur concernant l'interruption volontaire de grossesse (lois de 1975 et 1979).

Les trois comprimés de Mifépristone doivent être pris moins de 63 jours après le premier jour de vos dernières règles.

La Mifépristone ne doit pas être utilisée dans les cas suivants :

- si la grossesse n'est pas confirmée,
- en cas de suspicion de grossesse extra-utérine,
- si le premier jour de vos dernières règles date de 64 jours ou plus,
- si vous êtes âgée de plus de 35 ans et fumeuse (au moins 10 cigarettes par jour dans les 2 ans précédents),

CLINICAL STUDY SUMMARY
Product: Mifepristone

Protocol FF/92/486/24: Efficacy and Tolerance of Mifepristone (RU 486) Administered in a Single Dose of 600 mg in Association with Misoprostol as an Alternative for Vacuum Aspiration for Termination of Pregnancy with Amenorrhea of 63 Days or Less

1. Protocol Number: FF/92/486/24 **2. Study Design:** Open-label, phase III study of the single dose of 600 mg mifepristone followed by a dose of 0.4 mg misoprostol 36-48 hours later, and an additional dose of 0.2 mg misoprostol 3 hours later if complete abortion had not yet occurred. **3. Clinical Investigator:** Dr. Elizabeth Aubeny **4. Study Dates:** Start: November 1992 Completion: July 1993	**1. Age Range:** 15 - 51 years (mean 27.1) **2. Gestational Range:** 17 - 161 days (mean 51.7) - (calculated from 1148 patient responses) 31 - 63 days (mean 50.9) - (calculated from ultrasound for 629 patients) 31 - 69 days (mean 50.20) - (calculated from ultrasound when possible, otherwise from patient response for 1194 patients) **3. Patient Number:** Planned: 1000 Entered: 1194 Safety Evaluable: 1194 Efficacy Evaluable: 1104* Exposed to Study Drug: 1194 1164 (received mifepristone and misoprostol) 718 (received mifepristone and two doses of misoprostol) **82 patients were without confirmed pregnancy, 7 excluded for other non-compliance with protocol and 1 patient had conflicting data and outcome could not be determined.* **4. Test Drug:** Mifepristone Dosage: 3 x 200 mg (600 mg) Formulation: 200 mg tablet Duration of Dosage: One day **5. Control Treatment:** None **6. Ancillary Drug:** Misoprostol Dosage: 2 x 0.2 mg followed by 1 x 0.2 mg (if expulsion had not occurred within 3 hours) Formulation: 0.2 mg tablet Duration of Dosage: One day Interval from Study Drug: 36-48 hours	**1. Outcome Variables:** Tolerance and Safety: •Occurrence of painful uterine contractions, gastrointestinal and other adverse events with severity and need for treatment. •Level of pain using a visual analog scale (VAS). •Duration of uterine bleeding and the need for any additional treatments and/or procedures to control the bleeding. •Heart rate and blood pressure determined one hour after misoprostol administration and at the end of the post-misoprostol observation period. •Hemoglobin concentration and Rh status. Efficacy: •Evaluated by pelvic and ultrasound examinations and βHCG pregnancy tests. **2. Results:** Adverse Event: •A total of 3552 adverse events were reported in 1108 patients (997 of them during the 3 hours after the first dose of misoprostol.) •The most frequently reported were painful contractions, metrorrhagia, pelvic pain, nausea, vomiting and diarrhea. •Twelve patients required hospitalization for bleeding. Tolerance and Safety: •Mean VAS score for uterine pain was 33.8 ± 0.79 (sem). •Median duration of bleeding was 8 days. •There were minimal changes in mean values of vital signs for one hour after misoprostol administration and at the end of the observation period. •56 (5.4%) of patients had > 20% decrease in hemoglobin concentration. Efficacy: •Success rate for termination of pregnancy was 92.8%. •381 (38%) patients had complete expulsion within 3 hours after misoprostol.	**Status of Study:** **1. Study Classification:** Historically Controlled Studies - Mifepristone Plus Prostaglandin **2. Location of CRF's:** **3. Status of Database:** SAS files on disk **5. Status of Study Report:** Complete

CLINICAL STUDY SUMMARY
Product: Mifepristone

1. **Study Number:** FF/92/486/24

2. **Title:** Efficacy and Tolerance of Mifepristone (RU 486) Administered in a Single Dose of 600 mg in Association with Misoprostol as an Alternative for Vacuum Aspiration for Termination of Pregnancy with Amenorrhea of 63 Days or Less

3. **Study Dates:**
   Start: November 1992
   Completion: July 1993

4. **Clinical Investigator:** Dr. Elizabeth Aubeny
   Study Center: Hopital BROUSSAIS
   Centre d'Orhtogenie
   96, rue Didot
   75014 Paris

   Number of Centers Participating: 11
   Note: Unless otherwise indicated, this summary lists the first or Center # 1 investigator(s) found in the study report.

5. **Study Design:**
   Open-label, multicenter study of the single dose of 600 mg mifepristone followed by a dose of 0.4 mg misoprostol 36-48 hours later, and an additional dose of 0.2 mg misoprostol 3 hours later if complete abortion had not yet occurred.

6. **Study Population:**
   General Description of Population: Women requesting the interruption of pregnancy under the abortion law of France with confirmed intrauterine pregnancies.

   Age Range: 15 - 51 years (mean 27.1)

   Gestational Age Range: 17 - 161 days (mean 51.7) - (calculated from 1148 patient responses)
   31 - 63 days (mean 50.9) - (calculated from ultrasound for 629 patients)
   31 - 69 days (mean 50.2) - (calculated from ultrasound when possible, otherwise patient response for 1194 patients)

   Subject Numbers:
   Planned: 1000
   Entered: 1194
   Safety Evaluable: 1194
   Efficacy Evaluable: 1104*
   Exposed to Study Drug: 1194
   1164 (received mifepristone and misoprostol)
   718 (received mifepristone and two doses of misoprostol)
   **82 patients were without confirmed pregnancy, 7 excluded for other non-compliance with protocol and 1 patient had conflicting data where outcome could not be determined.*

7. **Study Drug:** Mifepristone
   Dosage: 3 x 200 mg (600 mg)
   Formulation: 200 mg tablet
   Duration of Dosage: One day

8. **Control Treatment:** None

9. **Ancillary Drug: Misoprostol**
   Dosage: 2 x 0.2 mg (0.4 mg) followed by 1 x 0.2 mg *(if expulsion had not occurred within 3 hours)*
   Formulation: 0.2 mg tablet
   Duration of Dosage: One day
   Interval from Study Drug: 36 - 48 hours

10. **Outcome Variables:**

Tolerance and Safety:
The occurrences of adverse events (including any concomitant illnesses) were monitored prior to the misoprostol administration and at the scheduled follow-up evaluation on days 10-18. The adverse events were characterized by their severity, onset, duration, need for treatment, outcome and relationship to mifepristone and misoprostol.

The occurrence and severity of painful uterine contractions and gastrointestinal adverse events were monitored during the 3 hours following the first dose and during the 2 hours after the second dose of misoprostol.

During the 4-5 hour observation period after misoprostol administration, adverse events other than painful uterine contractions and gastrointestinal events also were recorded. At 3 hours after the first dose of misoprostol and at 2 hours after the second dose, patients indicated their level of pain according to a visual analog pain scale (VAS).

Hemoglobin level and Rh status were determined at study entry and hemoglobin level was also determined before the day 10 - 18 visit. Duration of uterine bleeding and the need for any additional treatments and/or procedures to control the bleeding were evaluated at the day 10-18 visit.

Heart rate and blood pressure were measured at one hour after misoprostol administration and at the end of the post-misoprostol observation period.

Efficacy:
Pelvic examinations were performed before mifepristone administration, before misoprostol administration and at the day 10-18 evaluation. Uterine ultrasound examinations and quantitative βhCG subunit pregnancy tests were performed (at the discretion of the investigator) at the day 3 and day 10-18 clinic visits to document the progress of the pregnancy termination procedure.

11. **Statistical Methodology:**

Inferential and statistical methods were employed to analyze the data.

12. **Results:**

Adverse Events:
A total of 3552 adverse events (1108 patients) were reported for the 1194 patients. Adverse events were reported for 9 (30%) patients who received only mifepristone, for 412 (92%) patients who received mifepristone and a single dose of misoprostol, and for 687 (96%) patients who received mifepristone and two doses of misoprostol.

Translation from French

EFFICACY AND TOLERANCE OF MIFEPRISTONE (RU 486) ADMINISTERED IN A SINGLE DOSE OF 600 mg IN ASSOCIATION WITH MISOPROSTOL AS AN ALTERNATIVE FOR VACUUM ASPIRATION FOR TERMINATION OF PREGNANCY WITH AMENORRHEA OF 63 DAYS OR LESS

ROUSSEL HEALTH, RESEARCH AND DEVELOPMENT
Protocol FF/92/486/24

Circled items indicate those

for Aubeny,

APPENDIX C
ROUSSEL LABORATORIES PROTOCOL FF/92/486/24
PROTOCOL COVER SHEET

Study Phase: III

Name of Drug: Mifepristone
Active Ingredient: Mifepristone
Dosage: 600 mg
Route of Administration: Oral
Duration of Treatment: Single dose

Objective: To evaluate the efficacy, tolerance, and safety of 600 mg mifepristone followed by 0.4 or 0.6 mg misoprostol 36-48 hours later for the termination of pregnancies in women whose duration of amenorrhea was no more than 63 days.

Patient Population: Women aged 18-35 who were ≤ 63 days from onset of their last menstrual period and who requested termination of pregnancy.

Structure: Single group
Multicenter: Yes
Number of Centers: 11
Common Training: Yes
Blinding: None
Method of Patient Assignment: All patients were assigned to treatment with 600 mg mifepristone and 0.4-0.6 mg misoprostol

Concurrent Control: None

Estimated Total Sample Size: 1000

Statistical Rationale Provided: No

Primary Efficacy Variable: Proportion of patients with complete expulsion of the products of conception.

Adverse Reactions: Volunteered

Plan for Data Analysis: None

C. Protocol with Amendment and Case Report Form

(English Translations and Original Language Documents)

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THERAPY AREA
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PRO.October 92

FINAL VERSION

PROTOCOL FF/92/486/24

EFFICACY AND SAFETY OF MIFEPRISTONE (RU 486) ADMINISTERED AT THE DOSE OF 600 MG IN A SINGLE ADMINISTRATION IN COMBINATION WITH MISOPROSTOL AS AN ALTERNATIVE TO UTERINE ASPIRATION FOR TERMINATION OF PREGNANCY AGED LESS THAN OR EQUAL TO 63 DAYS OF AMENORRHEA

OPEN MULTI-CENTER STUDY

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TABLE OF CONTENTS

TABLE OF CONTENTS cont'd

1. INTRODUCTION

Mifepristone is an anti-progesterone compound synthesized by ROUSSEL UCLAF. Prior studies have shown that it is capable, by itself, of terminating about 80% of pregnancies aged less than or equal to 41 days of amenorrhea (1) when it is given at the dose of 600 mg orally in a single administration. After that date, the efficacy of the product by itself diminishes rapidly (about 10% drop in success rate per week of additional amenorrhea). Swedish (2), Scottish (3) and French (4-5) studies have shown that combining Mifepristone with a low dose of a synthetic prostaglandin analog (sulprostone 0.25 mg or Gemeprost 1 mg) enables termination and complete expulsion of the pregnancy in 95% of the cases for amenorrhea ranging up to 49 days.

The optimum period between the administration of Mifepristone and the administration of the prostaglandin is 36 to 48 hours. Indeed, the cervical dilation induced by Mifepristone is greater at 48 hours than it is at 24 hours, and the sensitivity to the uterine muscle to the contracting effects of prostaglandins is maximal 36 to 48 hours after the administration of Mifepristone (6, 7).

Mifepristone was registered in France in December 1988 as a medical alternative to uterine aspiration of pregnancy up to 49 days of amenorrhea; the rules of prescription at that time recommended the administration of 600 mg (3 tablets of 200 mg) of Mifepristone, in a single administration on day 1, followed 36 to 48 hours later by the administration of 1 mg of Gemeprost (Cervageme®) vaginally or 0.25 mg of Sulprostone (Nalador®) by intramuscular injection. The efficacy of the method (termination and complete expulsion of the pregnancy) was about 95%.

During the 4 hours following the prostaglandin, the adverse effects most often reported were painful uterine contractions in about 80% of the women, nausea in 34%, vomiting in 15%, diarrhea in 7.5% and discomfort in about 1% (5).

The other adverse effects most often reported, after the 4-hour period following the prostaglandin, were painful uterine contractions (1.6%), headache (1%), digestive problems: nausea (0.8%), vomiting (0.5%) and skin eruptions (0.2%) (8). Uterine bleeding necessitated a hemostatic endouterine procedure in 0.8% of the cases, and a transfusion in 0.1% of the cases.

Of all the women who used the method (about 80,000), 3 severe adverse effects of the myocardial infraction type were reported; the result was fatal in one case. These infarctions seem to be correlated with a coronary spasm and all occurred within 4 hours after sulprostone was injected. The 3 patients involved were all over 30 years of age and smoked. Those coronary spasms are attributable to sulprostone. They were also described after isolated injection of sulprostone (9) and resulted in the withdrawal of the intramuscular form of Sulprostone.

In view of those occurences, the decision was made to research whether prostaglandins other than the ones studied previously could be combined with Mifepristone.

Misoprostol is a synthetic derivative of the PGE_1 series (15-deoxy 16-hydroxy 15 methyl analog) administered orally at the dose of 4 tablets of 0.2 mg per day for the treatment or prevention of ulcerous duodenal or gastric lesions (10).

This product is widely prescribed and no serious cardiovascular effect has been published to date. The surveillance data is favorable (11).

In spite of an essentially digestive tropism, Misoprostol retains an effect of stimulating the uterine muscle (12, 13) and is therefore contraindicated in its current indication for pregnant women or for women who are heterosexually active with no effective method of contraception.

One study conducted in France involving 500 women, showed that 600 mg of Mifepristone, followed 48 hours later by 2 tablets of Misoprostol, enabled the termination and complete expulsion of 96.9% of pregnancies (95% confidence interval risk: 94.1 - 97.7%) up to 49 days of amenorrhea (14). Expulsion occurred on average 12 hours after the administration of Misoprostol; 61% of the women expelled within 4 hours following that administration and 87% within 24 hours. The average duration of uterine bleeding was 8.7 days. The average decrease in the hemoglobin concentration between the day of administration of Mifepristone and the follow-up visit was 0.7 g/dl. These results are similar to what was observed with gemeprost or Sulprostone. During the 4 hours following the administration of Misoprostol, 80% of the women reported painful uterine contractions that necessitated minor analgesic treatment in 20% of the cases. During that same period, the other adverse effects most often reported were nausea in 43% of the cases, vomiting in 17% and diarrhea in 14%. These symptoms very rarely required treatment. After the 4 hour period following administration of Misoprostol, the undesirable effects most frequently observed were nausea (4.3%), headache (4.2%), painful uterine contractions (3.2%), vomiting (3.0%) and asthenia (2.6%).

These results supported the registration of mifepristone/misoprostol combination in France in May 1994 for the termination of pregnancy up to or equal to 49 days of amenorrhea.

Another French study conducted, according to a similar protocol in 229 patients, showed that ovular expulsion occurred in 60.1% of the women, within 3 hours following the administration of 2 tablets of Misoprostol. Expulsion occurred between the 3rd and 4th hours in 14.6% of the cases. The 55 patients who did not expel after 4 hours : [redacted] and remained under observation for 2 additional hours. Thirty of them, i.e. 13.7% of all patients, experienced complete expulsion during the 2 hours of observation.

Thus, with this method [redacted] n terms of the dose of Misoprostol administered, ovular expulsion occurred at the Center in 88.4% of the women. The success rate in this study was 99.6%, and there was only one failure (placenta retention).

Safety was judged to be satisfactory, in terms of intensity of pain and in terms of bleeding.

In Great Britain, Mifepristone was registered in combination with Gemeprost (1 mg) for the voluntary termination of pregnancy up to 63 days of amenorrhea. Indeed, in a study in 957 women (15) requesting the termination of a pregnancy of up to 63 days of amenorrhea, the overall success rate was 94.8% (95% confidence interval: 93.4 - 96.2%). In this study, the success rate did not differ significantly according to the age of the pregnancy: less than 50 days of amenorrhea or from 50 to 63 days of amenorrhea.

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A hemostatic endo-uterine procedure and a blood transfusion had to be performed in 7 women (0.7%) due to copious bleeding. The average blood loss was measured at 1 center in 114 women and was 75.5 ml (range: ———ml). This is similar to the blood loss observed in surgical termination of pregnancy (16). The decrease in hemoglobin observed between the date of administration of Mifepristone (D1) and the follow-up visit on day 10 was less then or equal to 0.2 g/dl in 95% of the patients. The adverse effects were similar to those observed in the other studies.

In ——— one investigator also studied the efficacy of Mifepristone in combination with Misoprostol (3 tablets) in 100 women requesting termination of a pregnancy aged less than or equal to 56 days of amenorrhea (17). The success rate was 93% regardless of the age of the pregnancy: less than 50 days of amenorrhea or from 50 to 56 days of amenorrhea. Safety of the method was satisfactory. An endo-uterine procedure was necessary in 1 case and there was no transfusion. The average decrease in hemoglobin concentration between the date of administration of Mifepristone (D1) and the follow-up visit (D8) was 0.7 g/dl.

Considering these data, we propose to evaluate the efficacy of Mifepristone (600 mg) in combination with Misoprostol administered at the dose of 0.4 mg (2 tablets) or 0.6 mg (3 tablets) if necessary, in the termination of pregnancy aged less than or equal to 63 days of amenorrhea, to evaluate:

- whether the results observed in ——— can be applied to a prostaglandin other than Gemeprost; this would make it possible to standardize the rules for prescribing Mifepristone in France and Great Britain.

- whether, with no expulsion within 3 hours following administration of the first 2 tablets of Misoprostol, the administration of a 3rd tablet increases the percentage of expulsion during the observation phase in the center and perhaps the efficacy of the method.

2. PURPOSE OF STUDY

The purpose of this study is to evaluate the efficacy and safety of a single administration of 600 mg of Mifepristone, in combination with 2 or 3 tablets of 0.2 mg of Misoprostol, administered 36 to 48 hours later, for termination of pregnancy less than or equal to 63 days of amenorrhea, under the law on voluntary termination of pregnancy in France.

3. DESCRIPTION OF STUDY

This is an open multicenter study that will be conducted in 11 centers. The protocol is as follows:

* on day 1, in the investigator's presence, once the inclusion criteria have been verified:

  administration of 600 mg of Mifepristone (3 tablets)

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- On day 3, i.e. 36 to 48 hours after the administration of Mifepristone:

  Administration of 2 tablets of 0.2 mg of Misoprostol in a single administration, in the investigator's presence.

  The woman is kept under observation for 3 hours.

  If, 3 hours after administration of 2 tablets of Misoprostol, expulsion has occurred, the women are kept under observation for 1 additional hour.

  If, 3 hours after administration of 2 tablets of Misoprostol, expulsion has not occurred, the investigator will administer a third tablet of Misoprostol to the patient. The patient will be kept under observation in the hospital for 2 additional hours.

The efficacy and safety of the treatment will be evaluated 10 to 18 days after the administration of Mifepristone, during a follow-up visit.

4. SELECTION OF SUBJECTS

4.1 NUMBER OF SUBJECT NECESSARY

Considering the success rate observed in [redacted] in the trial involving 957 women, we anticipate including 1,000 patients in this study. This will enable a reasonable evaluation of efficacy and safety.

4.2 INCLUSION CRITERIA

The following will be included: women who

- request voluntary termination of pregnancy,
- meet the mandatory statutory requirements for voluntary termination of pregnancy in France,
- are at least 18 years of age (legal age of consent; underage women can be included only with the consent of their legal guardian),
- agree to submit to the constraints of the study, specifically the follow-up visit following administration of the treatment,
- are informed of the usual procedure for a miscarriage,
- agree to undergo a surgical termination of pregnancy should the treatment fail,
- are informed of the study procedure and have given their written consent to participate in it (appendix 1),

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and whose pregnancy is:

- intra-uterine,
- ongoing,
- aged less than or equal to 63 days of amenorrhea (calculated from the first day of the last menstruation).

If there is any doubt as to the localization of the pregnancy (clinical anomalies or discordance of ßHCG rates) or tubular history, an ultrasound will be done to make sure that the pregnancy is indeed intra-uterine and that it seems to be ongoing.

(The occurrence of an IUD pregnancy is not a contraindication provided that it is removed when Mifepristone is administered).

4.3. EXCLUSION CRITERIA

The following will not be included: women who

- have signs of spontaneous miscarriage in progress,
- have a suspicion of extra-uterine pregnancy,
- whose amenorrhea is greater than 63 days,
- are more than 35 years of age and smoke (this criterion will be defined as smoking at least 10 cigarettes per day for 2 years preceding the start of the study)
- have the following pathologies: cardiovascular history (angina pectoris, rhythm disorder, cardiac insufficiency, severe hypertension), asthma, glaucoma or high intraocular pressure, diabetes, hyperlipemia.
- have a renal, adrenal or hepatic insufficiency at the time of inclusion or in their history,
- have been treated with corticoids chronically within the preceding six months,
- have a known anomaly of hemostasis or are receiving anticoagulant treatment,
- have a known allergy to Mifepristone or Misoprostol
- have an anemia,
- refuse to give their written consent to participate,
- may not adhere to the requirements of the protocol, or who live very far from the center.

5. TREATMENT

5.1. MIFEPRISTONE

The Mifepristone will be supplied by ROUSSEL UCLAF in the form of tablets with 200 mg of micronized active ingredient.

The treatment will include 3 tablets packaged in bottle form.

The product will be given in a single administration of 3 tablets, in the medical investigator's presence, on an empty stomach.

The bottles of Mifepristone will be labeled as follows:

- Protocol No.
- Mifepristone
- Institute ROUSSEL ULCAF
- Batch No. - Expiration Date
- Patient No. (from 0001 to)

5.2 MISOPROSTOL

Misoprostol (Cytotec®) will be packaged in bottle form with 1 and 2 tablets of 0.2 mg and will be supplied by ROUSSEL UCLAF.

Each patient's treatment will consist of 2 bottles: one containing 2 tablets of Misoprostol and the other containing just 1 tablet.

The treatment will be administered as follows:

- 2 tablets of 0.2 mg of Misoprostol (1st bottle) in a single administration, 48 hours after the administration of Mifepristone, in the investigator's presence. The women will be kept under observation at the center for 4 hours.

- If expulsion does not occur within 3 hours following administration of Misoprostol, the investigator will administer a 3rd tablet (2nd bottle) of 0.2 mg to the patient. The patient will be kept under observation for 2 additional hours.

The bottles of Misoprostol will be labeled:
- Protocol No.
- Misoprostol
- Institute ROUSSEL UCLAF
- Batch No. - Expiration Date
- Patient No. (from 0001 to)

Bottle No. 1 (for the bottle containing 2 tablets)
or Bottle No. 1 (for the bottle containing 1 tablet)

All 3 bottles of Mifepristone and Misoprostol representing a patient's treatment will be placed together into a box labeled:
- Protocol No.
- Mifepristone - Misoprostol
- Institute ROUSSEL UCLAF
- Patient No. (from 0001 to)

5.3. MANAGEMENT OF PRODUCTS

All treatments necessary for a center will be given to the pharmacist in charge of that center, who will see to it that they are distributed to the investigator.

After verifying the inclusion and exclusion criteria, the women will be assigned a number for admission to the study and will be given a box bearing that number. The numbers will be assigned in order.

A drug disposition sheet of the product under study must be kept up to date by the investigator.

At the end of the study, all of the unused product, and the drug disposition sheet, must be recovered by the monitor.

5.4. CONCOMITANT TREATMENT

5.4.1 Authorized Treatments

Insofar as possible, no other treatment will be used. If a prescription is written, the type and dose of the medication will be indicated on the case report form.

Treatments in progress will be indicated on the case report form.

5.4.2 Prohibited Treatments

- Acetylsalicylic acid and derivatives thereof, steroidal or non-steroidal anti-inflammatories, prostaglandin synthesis-inhibiting medications (if necessary, an analgesic of another pharmacological class or an antispasmodic will be used in preference over those medications), enzyme-inducing medications.
- Oxytocic or prostaglandins other than the one used in the study.
- The patient must abstain from any self-medication.
- The patient must abstain from smoking or drinking alcohol during the 48 hours between the administration of mifepristone and the administration of misoprostol, and on the day misoprostol is administered.

6. EVALUATION CRITERIA

6.1 EFFICACY

Efficacy will be evaluated 10 to 18 days after the administration of Mifepristone (D10 - D18) by the investigator based on clinical (occurrence of bleeding, expulsion of egg sac, persistence of bleeding), biological and/or ultrasound data.

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The following will be distinguished:

1 - Termination of the pregnancy and complete expulsion (disappearance of clinical signs, drop in ßHCG compared to day 1 and/or empty uterus if ultrasound is done) with no need for additional surgical procedure (aside from possible extraction with forceps of ovular fragments protruding from the external orifice of the cervix). The expulsion date and, if possible, the time of expulsion will be noted, as well as the number of tablets of Misoprostol administered. This outcome will be considered a success.

2) Termination of the pregnancy without complete expulsion.

3) Persistent pregnancy.

4) Need for a hemostatic endo-uterine procedure.

Outcomes 2, 3 and 4 will be followed by an additional surgical procedure, the date of which will be noted. They will be considered failures.

6.2. SAFETY

6.2.1 When misoprostol is administered (day 3):

Safety will be evaluated based on:

* Any adverse effect occurring from day 1 (administration of Mifepristone) and day 3.

* The occurrence of painful uterine contractions and digestive problems: nausea, vomiting, diarrhea during the hours of observation at the Center after administration of the first 2 tablets and if necessary the 3rd tablets of Misoprostol. The intensity of these symptoms will be noted as will the need for any symptomatic treatment.

* Measurement of blood pressure (systolic and diastolic) and heart rate, one hour after the 1st administration of Misoprostol and at the end of the observation period.

* The occurrence of an adverse effect other than the ones cited above.

6.2.2 At the time of the follow-up visit (D10 - D18):

Safety will be evaluated based on:

* The duration of uterine bleeding and the need for special measurements: measurement of hemoglobin concentration, medical treatment, blood transfusion, hemostatic surgical procedure.

* Any unusual clinical sign or symptom occurring since day 3.

6.2.3 Biological Safety

This will be evaluated based on the hemoglobin concentration measured on day 1 (before administration of Mifepristone) and on day 10 to day 18 at the time of the follow-up visit.

7. PROCEDURE OF TRIAL

7.1. Day 1: INITIAL EVALUATION

Verify that the patient has taken the legal measures to request voluntary termination of pregnancy and meets the conditions set by the law (reflection period).

- Note:
  - the primary history,
  - any treatment currently in progress and the reason for it,
  - the date of the last menstruation.
- Verify that the age of the pregnancy is less than or equal to 63 days of amenorrhea.
- Measure the ßHCG and/or do a uterine ultrasound (ultrasound is mandatory if there is any doubt as to the localization of the pregnancy or a tubal history).
- Determine the Rh factor if the patient has no group card, and measure the hemoglobin concentration.
- Give the patient an information sheet on the study and obtain her written consent to participate.
- Assign the woman a study admission number and give her 3 tablets of Mifepristone contained in the box bearing that number. The treatment will be taken immediately in the investigator's presence. The number will be noted on the case report form.
- Inform the women that she must abstain from smoking or drinking alcohol for the next 48 hours and on day 3.
- Make an appointment for the morning two days later (day 3).

7.2. DAY 3: ADMINISTRATION OF MISOPROSTOL:

- Clinical examination.
- Look for any adverse event.
- Do an injection of anti-D-gamma globulins if the patient is Rh negative.
- Administer 2 tablets of 0.2 mg of misoprostol in a single administration (if the expulsion has not already occurred) in the investigator's presence.

- The patient must remain under observation at the center for the following 3 hours.
- During those 3 hours of observation, the following parameters are evaluated:
  * Painful uterine contractions, nausea, vomiting, diarrhea, using the following scale:

1: minimal
2: moderate
3: intense

It will also be evaluated whether these symptoms require treatment.

- The overall intensity of the pain during that observation will also be evaluated on an analog visual scale 3 hours after administration of misoprostol,
- if a premedication has been given, it will be noted on the case report form.
- The treatment administered will be noted on the case report form.
* The heart rate, blood pressure (systolic and diastolic) will be measured one hour after the 2 Misoprostol tablets are administered.

If, 3 hours after administration of the first 2 tablets of Misoprostol, expulsion (verified by the investigator) has occurred:

* The woman will be kept under observation for one additional hour.
* The systolic and diastolic blood pressure, and heart rate will be measured at the end of the observation period.

If, 3 hours after administration of the first 2 tablets of Misoprostol, expulsion has not occurred:

* Perform gynecological examination to verify that the egg sac is not present in the cervix or the vagina and extractable with forceps.
* If non-expulsion is confirmed, give the patient a 3rd tablet of Misoprostol and keep her under observation for 2 additional hours.
* During those 2 hours, evaluate the same parameters as defined above. The systolic and diastolic blood pressure, and heart rate will be measured at the end of the observation period.
- The time of ovular expulsion will be noted if it occurs while the patient is under observation.

- If the patient has chest pain, cardiac rhythm disorder or low blood pressure, an EKG must be done. If the pain is severe, fast-acting nitrate derivatives will be prescribed for the outcome coronary spasm.

- After 4 to 5 hours, as the case may be, the woman is authorized to leave the center and is given an appointment for D10 - D18, with a prescription for a hemoglobin test to be taken just prior to the next visit.

- An oral contraception to begin 24 to 48 hours later may be prescribed at that visit.

7.3. DAY 10 - DAY 18: FOLLOW-UP VISIT:

- New clinical examination and evaluation of safety by the investigator.

- If possible, note the date of ovular expulsion and the time lag with respect to the administration of prostaglandin.

- Final evaluation of the efficacy of the treatment (by clinical examination data, ßHCG and/or ultrasound).

- If the patient has started an oral contraceptive before this follow-up visit, note the name of the contraceptive prescribed.

- Evaluation of metrorrhagia:

  - duration,

  - was there any need for an emergency measurement of the hemoglobin concentration (note the result)?

  - was there any need for a treatment (medication, transfusion, hemostatic surgical procedure)?

- If the event of failure (continuing pregnancy, incomplete expulsion), recommend an additional surgical procedure (this procedure must not be done before day 10 unless medically justified).

- Note the results of the hemoglobin measurement.

8. COLLECTION AND ANALYSIS OF DATA

8.1. COLLECTION OF DATA

A case report form will be filled out for each patient admitted to the study. Only the investigator and his/her coworkers are authorized to fill out the case report form and make any corrections in it.

Any correction on the case report form must be made by drawing a line through the incorrect data so that it remains visible, and putting the corrected data alongside it. The person making this correction must enter the date and initial it in the margin. Each case report form must be signed and dated by the investigator.

8.2. STATISTICAL ANALYSIS:

8.2.1 Efficacy Analysis

Since this is a non-comparative study, the analysis of the data will be descriptive. The main criterion of efficacy will be the estimated success rate on day 10 to day 18. The data will be stratified based on the age of the pregnancy: up to 49 days of amenorrhea, and from 50 to 63 days of amenorrhea. The 2nd criterion of efficacy will be the percentage of expulsions during observation at the Center.

8.2.3 Safety Analysis

A descriptive analysis of the safety will be done overall, then categorized acoording to the age of the pregnancy (up to 49 days of amenorrhea, from 50 to 63 days of amenorrhea).

For hemoglobin, variations with respect to the inclusion values will be tested by a variance analysis.

9. AMENDMENTS TO PROTOCOL

There can be no changes in the protocol without written consent from ROUSSEL UCLAF.

Any change must be the subject of an amendment documented and justified in writing. It must be signed by the investigatgor as acceptance of the change in the study procedure.

This amendment to the protocol must be submitted to and approved by the Consulting Committee for Protection of Persons in Biomedical Research if it is able to modify the ratio of expected-medical-benefit/risk to the patient unfavorably.

If the change in the protocol is necessary immediately to assure patient safety, the persons in charge of the study will submit the amendment to the CCPRB after its acceptance, but as soon as possible.

10. ADVERSE EVENTS

CLINICAL SAFETY

1) ADVERSE EVENT

1.1 Definition:

The term adverse event includes any intercurrent events (or diseases), medical reactions, clinical or biological anomalies that the investigator considers pertinent.

1.2 **Procedure to be followed:**

Any adverse event occurring during the clinical trial, whether or not it is correlated with the drug studied, will be reported and analyzed by the investigatgor on the adverse-event page of the case report form.

To document adverse events as well as possible, the investigator will follow the guide published by the Central Division of Surveillance (procedure to be followed in the event of clinical or biological anomalies during the clinical trial - see corresponding publication).

2) SERIOUS ADVERSE EVENT:

2.1 **Definition:**

According to the FDA (Food and Drug Administration), a serious adverse event is any event that:

- causes death
- threatens the life prognosis
- involves sequelae or becomes chronic
- requires or lengthens the hospitalization
- results in an overdosage
- any cancer or congenital anomaly discovered during the trial

ROUSSEL UCLAF adheres to this definition.

2.2 **Procedure to be followed:**

Any serious adverse event occurring under treatment or during the first 2 weeks following the end of treatment, will be reported within 24 hours to the monitor of the trial even if the investigator feels that the adverse event is not correlated with the treatment.

MONITORS

· Name		Dr. V. Targosz or
	ROUSSEL UCLAF	ROUSSEL Laboratories
· Address	102, route de Noisy 93230 ROMAINVILLE	97, rue de Vaugirard 75006 Paris
· Telephone		
· Fax		
· Telex	ROUS 235 477 F	GRUPA 200 675 F

In the monitor's absence, the investigator will notify the Surveillance Department directly.

ROUSSEL UCLAF
Surveillance Department
102, route de Noisy
93230 ROMAINVILLE

Telephone:
Fax:

The initial notification will be by telephone, fax or telex and must include:

- the investigator's identification: name, address, title, center No.
- Protocol No.
- the patient's identification (initials, number assigned in the study, age).
- the dates of administration of Mifepristone and Misoprostol
- description of the adverse event and its onset date.
- measures taken.
- the investigator's opinion as to the correlation with the treatment, if possible at that stage.

As soon as possible (within 3 days maximum), as confirmation, the investigator will fill out the serious adverse event form (Appendix 2). This document will be signed by the investigator and sent by fax or express mail to the monitor of the trial. As soon as possible, the investigator will send all the pertinent information on the serious adverse event (evolution, precise description of the medical history, results of research, copy of hospitalization report, autopsy, etc.) and will evaluate the correlation to the treatment.

To respect current law on reporting serious adverse events to the heath authorities and enable the Surveillance Department to analyze the safety of the molecules developed, the investigator agrees to document the adverse event as well as possible, to respect the reporting deadlines, to furnish the Surveillance Department with all information necessary for analyzing the event, and if necessary, authorizes it to access the source data.

In addition to the appropriate protocol measures, a plasma sample will be taken if possible.

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Five milliliters of blood will be taken on a heparinate tube. After centrifuging, the plasma will be placed in a dry tube; labeled (protocol No., patient No., initials, data and time sample was taken) and frozen as soon as possible.

BIOLOGICAL SAFETY

Any clinically significant anomaly will be documented as soon as possible so that it can be analyzed (see publication "procedure to be followed when anomalies occur during a therapeutic trial"). The biological parameter will be monitored until it normalizes.

11. PATIENTS LOST TO FOLLOW UP AND WITHDRAWN FROM TRIAL

All patients admitted to the study will be analyzed for safety. Only women who finish the trial can be analyzed for efficacy.

12. NOTIFICATION OF AUTHORITIES

The study will be reported to the Ministry of Health.

13. ETHICS

This study will be conducted according to the principles of the Helsinki Declaration (see appendix 3) and pursuant to French law on clinical trials.

13.1 CONSENT:

Before the patient is included in the trial, her written consent will be obtained on a triplicate form (signed by the patient and preceded by the notation "read and approved"). To obtain that consent, an informative document on the study in which she is to participate will be given to her (appendix 1).

The investigator will also sign a form for identification consent "thereby attesting that the patient's consent has been obtained."

13.2 CONSULTING COMMITTEE FOR PROTECTION OF PERSONS IN BIOMEDICAL RESEARCH (CCPPRB):

The protocol will be submitted to a Consulting Committee for Protection of Persons in Biomedical Research (CCPPRB).

The study may not begin until after ROUSSEL UCLAF has received a copy of that committee's written agreement.

Any amendment in the protocol, any change in the project that substantially affects the information furnished to the CCPPRB will be the subject of an additional request for opinion.

14. CONFIDENTIALITY

The data collected during this study will be considered confidential.

The information furnished by ROUSSEL UCLAF (drug brochure, protocol, case report form) are also confidential.

For each patient, the data will be identified by the patient's number in the study and by her initials, and will be treated anonymously in the analyses.

All data relative to this study must be kept available to the other participating investigators, the ROUSSEL UCLAF Coordinator, the Head of ROUSSEL UCLAF Quality Control, the CCPPRB, and the Oversight Authorities.

15. STUDY FOLLOW-UP AND QUALITY CONTROL

Members of ROUSSEL UCLAF will be in regular contact with the investigator by on-site visits and telephone calls to monitor the progress of the study and make sure that it is conducted in accordance with the protocol.

The case report form will be reviewed in detail at the time of each visit.

The investigator and his team cooperate with the monitor, to give the monitor access to the source documents, and specifically to provide the monitor with missing information whenever possible.

Each case report form will be signed by the investigator. The investigator must initial and date all corrections.

If any data is missing or unavailable, the reason must be stated.

Participation in this study means that the investigator accepts the possibility of a Quality-Control audit to verify that the procedures described in the protocol have been followed throughout the study.

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16. DURATION OF THE STUDY

The study will start in November 1992 and last about 1 year.

17. INSURANCE

The investigator's civil liability under this study is covered by insurance purchased by ROUSSEL UCLAF (appendix 4).

18. PUBLICATION

Any presentation or publication of the results of this study must first be agreed upon between the investigators and ROUSSEL UCLAF.

19. INVESTIGATOR'S COMMITMENT AND LIABILITY

All information on the product being tested and the results of the study are considered confidential.

I have read the protocol and I feel that it contains all the information necessary for conducting the trial.

I undertake to conduct this trial in accordance with the protocol; I will not make any change in it without the written consent of ROUSSEL UCLAF.

I undertake not to start this study until a CCPPRB has given its agreement.

I will conduct this trial according to the principles set forth in the Helsinki Declaration, and in conformity with Good Clinical Practice; particularly, I will obtain the written Informed Consent of each patient before she enters the study.

I further undertake to write the case report form carefully, to respect the procedure in the event of serious side effect and to monitor the management of the product being tested.

I accept that the study will be monitored by a member of ROUSSEL UCLAF as well as the outcome of a Quality-Control audit.

I will keep all data and information directly concerning this study available to ROUSSEL UCLAF and the Oversight Authorities.

I will retain the rough data collected during this study for a period of 15 years.

Product name: Mifepristone
Protocol No.: FF/92/486/24

Date Signature of Investigator

Date Signature of ROUSSEL UCLAF Coordinators

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CHECK - LIST

Day 1: INCLUSION:

- Confirmed, normal pregnancy,
- Request for voluntary termination of pregnancy, legal formalities fulfilled,
- Amenorrhea less than or equal to 63 days,
- Age greater than or equal to 18 years (or authorization from legal guardian for minors),
- Absence of contra-indication for the method,
- Explain to patient what happens in a miscarriage and the terms of the protocol; obtain written consent,
- Assign her a number corresponding to her order of admission to the trial (the numbers will be assigned in order),
- Measurement of ßHCG and/or ultrasound,
- Mandatory ultrasound in the event of any clinical or biological anomaly (ßHCG) or tubular history,
- Measurement of hemoglobin, blood group,
- In the investigator's presence, administer 3 tablets of Mifepristone contained in the box bearing the patient's number,
- Tell the patient that she is not to smoke or drink alcohol for the next 48 hours and on (D3),
- Appointment for (D3)

DAY 3: ADMINISTRATION OF MISOPROSTOL:

- Injection of anti D gamma globulins if the patient is Rh negative,
- Record any functional signs that have appeared since Mifepristone was administered,
- Verify that expulsion has not occurred between D1 and D3,
- If expulsion has not occurred, administer misoprostol: 2 tablets of 0.2 mg in a single administration,
- Observation for 3 hours after that administration:
  - One hour after the administration of Misoprostol, measure the systolic and diastolic blood pressure and the heart rate,
  - Check for painful uterine contractions, nausea, vomiting, diarrhea, evaluate their intensity and note any treatments administered,

- If expulsion occurs within 3 hours following administration of Misoprostol:
  - Keep the patient under observation for one additional hour.
  - Measure the blood pressure (systolic and diastolic) and the heart rate at the end of the observation period.
- If expulsion does not occur within 3 hours following administration of Misoprostol:
  - Perform a gynecological examination to make sure that the egg sac is not present in the cervix or the vagina and is extractable with forceps,
  - If confirmed that expulsion has not occurred, administer to the patient a 3rd tablet of Misoprostol and keep her under observation for 2 additional hours, measuring the same criteria as those stated above.
  - Measure the blood pressure (systolic and diastolic) and the heart rate at the end of the observation period.
- Note the time of the ovular expulsion, if it occurs at the Center.
- Appointment on D10 - D18, with a prescription for hemoglobin dosage.
- Possible prescription of an oral contraceptive to be started 24 to 48 hours later.

DAY 10 - DAY 18: FOLLOW-UP VISIT:

- Evaluation of efficacy and safety of treatment,
- If possible, note the date and time of the ovular expulsion,
- Note the results of the hemoglobin dosage,
- In the event of a failure (continuing pregnancy or uterine retention), recommend an additional surgical procedure (this procedure must not be done before day 10 unless medically justified).

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REFERENCES

1. Investigators Drug Brochure.

2. M. BYDGEMAN, M.L. SWAHN - Progesterone receptor blockade. Effect on uterine contractility and early pregnancy.
Contraception, 1985, 32 p. 45-51

3. M.W. RODGER, D.T. BAIRD - Induction of therapeutic abortion in early pregnancy with mifepristone in combination with prostaglandin pessary.
Lancet, 1987, 2, p. 1415-1418

4. C. DUBOIS, L. SILVESTRE, A. ULMANN - Use of Mifepristone in voluntary termination of pregnancy. French Experiment.
Presse Med., 1989, 18, p.757-760

5. L. SILVESTRE, C. DUBOIS, M. RENAULT, Y. REZVANI, E.E. BAULIEU, A. ULMANN - Voluntary interruption of pregnancy with mifepristone (RU 486) and a prostaglandin analogue. A large-scale French experience.
N. Engl. J. Med., 1990, 322, p. 645-648

6. Y. LEFEBVRE, L. PROULX, R. ELIE, O. POULIN, E. LANZA - The effects of RU 38 486 on cervical ripening. Clinical studies.
Am. J. Obstet. Gynecol., 1990, 162, p.61-65

7. M.L. SWAHN, M. BYDGEMAN - The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin.
Br. J. Obstet. Gynecol., 1988, 95, p. 126-134.

8. Report on study FFR/88/486/01 (Roussel Laboratories).

9. E. FLIERS, D. DUREN, P.A. VAN ZWIETEN - A prostaglandin analogue as a probable cause of myocardial infarction in a young woman.
Brit. Med. J. 1991, 302, 416

10. R.L. HERTING, C.H. NISSEN - Overview of misoprostol clinical experience.
Dig. Dis. Sci., 1986, 31, (suppl.), p. 47S-54S

11. R.A. WILDEMAN - Focus on misoprostol: Review of Worldwide safety data.
Clin. Invest. Med. 1987, 10, p. 243-245

12. T. RABE, H. BASSE, H. THURO, L. KIESEL, B. RUNNEBAUM - Effect of PGE_1 methyl analog, misoprostol on the pregnant uterus during the first trimester. Obstet & Gyneco., 1987, 47 : 324-331

13. J.E. NORMAN, K.J. THONG, D.T. BAIRD - Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone.
Lancet, 1991, 336 : 1233-1236

14. Study FFR/91/486/14 - Roussel Laboratories internal report.

15. Study UK/86/486/07 - Roussel Laboratories internal report.

16. D.T. BAIRD, M.W. RODGER, I.T. CAMERON, I. ROBERTS - Prostaglandins and antigestagen for interruption of early pregnancy.
J. Reprod. Fert. (suppl.), 1988, 36 : 173-179

17. K. JOO THONG, D.T. BAIRD - Induction of early abortion with Mifepristone and Misoprostol in early pregnancy. Submitted to Br. J. Obstet Gynaecol

APPENDIX 1

FORM OF INFORMATION INTENDED FOR PATIENTS

AND

WRITTEN INFORMED CONSENT

FORM OF INFORMATION INTENDED FOR PATIENTS

AND

WRITTEN INFORMED CONSENT

PROTOCOL No.: FF/92/486/24

TITLE OF STUDY: Efficacy and safety of Mifepristone (RU 486) administered at the dose of 600 mg in a single administration in combination with Misoprostol as an alternative to uterine aspiration for termination of pregnancy aged less than or equal to 63 days of amenorrhea

PATIENT No.:

You have requested a termination of pregnancy. It is proposed that you participate in a study intended to evaluate, on a wide scale, the efficacy of the combination of Mifepristone and an oral prostaglandin, misoprostol, in the voluntary termination of pregnancies of up to 63 days of amenorrhea.

This study complies with legislation on clinical trials and the principles of the Helsinki declaration: it was submitted to the Consulting Committee for Protection of Persons in Biomedical Research which issued a favorable opinion on October 6, 1992.

In May 1992, the Ministry of Health authorized the marketing of the Combination Mifepristone 600 mg + 2 tablets of Misoprostol for voluntary termination of pregnancies of up to 49 days of amenorrhea. This combination enables termination and complete expulsion of the pregnancy in 95% of the cases.

A British study, involving 957 women, has shown that the combination of Mifepristone and a prostaglandin given in vaginal suppository form maintained that same efficacy up to 63 days of amenorrhea.

Moreover, a preliminary study, conducted in France and involving 229 patients, has shown that the administration of a 3rd tablet of Misoprostol (if expulsion has not occurred within 3 hours following administration of the first 2 tablets) increased the overall success rate to 99%; moreover, with this type of protocol, expulsion occurred at the hospital center, i.e. before the end of the 4th hour, in 88.4% of the women.

Those 2 observations need to be confirmed on a wider scale and 1,000 women will participate in this study.

They will be recruited in 11 private or public hospital centers.

Mifepristone is a drug that blocks the effect of progesterone, the hormone that maintains pregnancy. However, its effect needs to be supplemented, 36 to 48 hours later, by a prostaglandin, a substance that increases uterine contractions.

Mifepristone can be used only in compliance with current regulations concerning voluntary termination of pregnancy (laws of 1975 and 1979).

The three tablets of Mifepristone must be taken less than 63 days after the first day of your last menstruation.

Mifepristone must not be used in the following cases:

- if the pregnancy is not confirmed,
- if extra-uterine pregnancy is suspected,
- if the first day of your last menstruation was 64 days ago or more.
- if you are older than 35 and smoke (at least 10 cigarettes per day for the previous 2 years),

- in the event of one of the following diseases: kidney insufficiency, liver insufficiency, adrenal insufficiency, anomaly of blood coagulation or administration of anticoagulant medication, anemia, asthma or history of asthma, cardiovascular history (angina pectoris, rhythm disorders, cardiac insufficiency, severe hypertension), diabetes, hyperlipemia, glaucoma or increased intraocular pressure,

- in cases of prolonged treatment with corticoids.

TERMINATION OF PREGNANCY BY MIFEPRISTONE HAS LIMITS AND INVOLVES CONSTRAINTS THAT YOU MUST BE FAMILIAR WITH

1) The administration of Mifepristone must be followed 36 to 48 hours later by the administration of a prostaglandin, to obtain the maximum efficacy of the method.

2) Mifepristone is not 100% effective, and you cannot judge the efficacy of the method on your own. The uterine bleeding that occurs is not proof of efficacy and expulsion of the egg, which often occurs a few hours after administration of prostaglandin, may be incomplete.

You must therefore submit to a follow-up visit, 10 to 18 days after administration of Mifepristone, to verify that your pregnancy has indeed terminated.

THE FOLLOW-UP VISIT IS FOR VERIFYING THAT THE PREGNANCY HAS BEEN TERMINATED. IF THE PREGNANCY CONTINUES AFTER MIFEPRISTONE AND PROSTAGLANDIN, THE FETUS OR CHILD TO BE BORN IS LIABLE TO BE DEFORMED.

In the event of a failure, the termination of pregnancy or evaluation of placenta debris can be obtained only by surgical means.

As in any termination of pregnancy, uterine bleeding (metrorrhagia) occurs in nearly all cases. It can sometimes be very copious and may necessitate emergency treatment. Therefore, you must not travel any great distance from the study center until the follow-up visit, and the physician will tell you where to call or go in the event of an emergency.

Abdominal pain requiring treatment, nausea, vomiting, diarrhea and discomfort occur in some cases after administration of the prostaglandin. Therefore, it must be followed by several hours of observation at the study center.

Another pregnancy is possible immediately after termination of the pregnancy: if you do not want another pregnancy, contraception must be started early.

If you are a Rh negative blood group, prevention of rhesus immunization must be done.

Exceptional cases of cardiovascular accidents have been reported after injection of a prostaglandin. Consequently, the Mifepristone-prostaglandin analog method is contraindicated when the cardiovascular risk is increased by the following factors: hyperlipemia, diabetes, severe high blood pressure, cardiovascular accidents, being over 35 years of age and smoking tobacco.

You must abstain from TOBACCO and ALCOHOL for the two days between administration of Mifepristone and administration of the prostaglandin, and on the day of administration of the prostaglandin. Furthermore, the study may be interrupted:

- for medical reasons to be judged by the physician,

- your own desire, and you are not required to furnish any justification.

An uterine evacuation may be done at your request and under medical control.

In emergencies and for any question regarding this study, you may contact by telephone:

Dr. at number:

or one of the Centers on the attached list.

Protocol No.: EF/92/486/24

I, the undersigned: _____

Residing at: _____

_____

certify that I have read the attached text entitled "Information intended for the patient" and agree to participate, fully informed and completely of my own free will, in the medical research conducted by Dr. _____

I agree that the data recorded in this study, including, considering the research needs, my ethnic background, may be processed on computer by ROUSSEL UCLAF. I have noted that the right of access provided by the "information and liberties" law (article 40) may be exercised at any time with Dr. _____

I may exercise my right of rectification with Dr. _____ through the physician of my choosing.

The data concerning my identity will remain strictly confidential. I authorize their consultation only by:

- persons who are working on the study, designated by the organizer Dr. Louise Silvestre

- and a representative of the Health Authorities.

My identity will not be revealed in any reports or publications to which this study may give rise.

I am aware of the possibility of refusing to participate in this study or withdrawing my consent at any time, with no responsibility on my part.

Assigned processing number

[city]

[date]

Date and signature of investigator

Signature of subject preceded by the notation "read and approved"

- Original for the patient;
- Second copy to be kept in a confidential overall envelope sealed by the investigator, to be given to Roussel Santé R&D at the end of the study.
- Third copy to be kept for at least 15 years by the investigator.

APPENDIX 2

CASE REPORT FORM SERIOUS ADVERSE EVENTS

SURVEILLANCE DEPARTMENT - ROUSSEL UCLAF

CLINICAL TRIAL
CASE REPORT FORM SERIOUS ADVERSE EVENTS

PROTOCOL/INVESTIGATOR

Protocol number
Center number

Indication

Name of investigator

Address

Country

PATIENT

Number assigned in study

Surveillance number (local)

Initials

Age
years months

Sex
M F

Weight
KG G

Height
M CM

Occupation

Ethnic background

Relevant history

Drug intolerances No Yes Unknown

Drugs involved

ADVERSE EVENT

Date of occurrence day month year

Description

Hospitalization (or extension of hospitalization) necessary? Yes No

Treatment

FINAL OUTCOME

Complete cure

Chronic or sequelae

Effects still existing

Unknown

Death

• Date
day month year

PROTOCOL NUMBER [ ]

PATIENT NUMBER [ ]

SUMMARY

(Precise description of medical history concerning the event)

APPEARS THIS WAY
ON ORIGINAL

Protocol number _____ Patient Number ☐

DRUG STUDIED

Name _____ Administration plan
or dose units frequency
Code ☐
Method of administration

Date of treatment
Start: ☐☐☐ End ☐☐☐ In progress ☐
day month year day month year

Administration of drug after start of side effect: Immediate results:

Continued same dose ☐ Interrupted ☐ Improvement ☐ No Change ☐ * NA ☐
Reduced ☐ *NA ☐ Aggravation ☐ Unable to interpret ☐

Readministration:
No ☐ Yes ☐ *NA ☐

Date ☐☐☐
Day Month Year

Reappearance of reaction:
No ☐ Yes ☐ *NA ☐

Unable to interpret ☐

*Not applicable

CONCOMITTANT DRUGS

Name	Dose/ 24 hours	Start date	End date	Indication

CAUSAL RELATIONSHIP

Investigator's opinion:

ruled out ☐ improbable ☐
possible ☐ probable ☐ very probable ☐
not able to evaluate ☐
explain why ☐

This sheet was filled out on ☐☐☐ Name of monitor and signature
day month year

by: _____

APPENDIX 3

HELSINKI DECLARATION

OF

WORLD MEDICAL ASSOCIATION

Declaration of Helsinki

Recommendations guiding medical doctors
in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964
and As Revised by the 29th World Medical Assembly, Tokyo, Japan, 1975.

Introduction

It is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the world, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies *a fortiori* to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to every doctor in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care
(Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic Biomedical Research Involving Human Subjects
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

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ROUSSEL UCLAF

AMENDMENT NO. 1
TO PROTOCOL FF/92/486/24

"Efficacy and safety of mifepristone (RU 846) administered at the dose of 600 mg in a single administration in combination with Misoprostol as an alternative to uterine aspiration for termination of pregnancies aged less than or equal to 63 days of amenorrhea"

This amendment concerns:

- the withdrawal of the following center:

[ ]

- and its replacement by the following center:

[ ]

We grant formal approval of this amendment.

For the Investigator: For the Sponsor:

APPEARS THIS WAY
ON ORIGINAL

Translation from French

EFFICACY AND TOLERANCE OF MIFEPRISTONE (RU 486) ADMINISTERED IN A SINGLE DOSE OF 600 mg IN ASSOCIATION WITH MISOPROSTOL AS AN ALTERNATIVE FOR VACUUM ASPIRATION FOR TERMINATION OF PREGNANCY WITH AMENORRHEA OF 63 DAYS OR LESS

ROUSSEL HEALTH, RESEARCH AND DEVELOPMENT
Protocol FF/92/486/24

ROUSSEL HEALTH, RESEARCH AND DEVELOPMENT
PRODUCT RU 38486
PROTOCOL NO FF/92/486/24

Center # ------- Patient # ---------- Date of visit----------

INCLUSION CRITERIA

(mark correct answer)

THE PATIENT MUST ANSWER "YES" TO ALL OF THE FOLLOWING QUESTIONS IN ORDER TO BE INCLUDED IN THIS STUDY.

- Requests termination of pregnancy — No___ Yes___
- Satisfies the legal requirements associated with voluntary termination of pregnancy under French law — No___ Yes___
- Is of 18 years of age or has parental consent — No___ Yes___
- Has normal intrauterine pregnancy of duration of 63 or less days of amenorrhea — No___ Yes___
- Accepts surgical termination of pregnancy in case of treatment failure — No___ Yes___
- Agrees to comply with the constraints of the study — No___ Yes___
- Is informed of development of events upon a threatened abortion — No___ Yes___
- Is informed about the nature of the study and willing to give her written consent to participate — No___ Yes___

ROUSSEL HEALTH. RESEARCH AND DEVELOPMENT
PRODUCT: RU 38486
PROTOCOL NO. FF/92/486/24

Center #_____ Patient #_____ Date of visit_____

EXCLUSION CRITERIA
(mark correct answer)

THE PATIENT MUST ANSWER "NO" TO ALL OF THE FOLLOWING QUESTIONS IN ORDER TO BE INCLUDED IN THIS STUDY

- Shows signs of threatened abortion — No___ Yes___
- Suspicion of an ectopic pregnancy — No___ Yes___
- Has amenorrhea of more than 63 days — No___ Yes___
- Has adrenal deficiency — No___ Yes___
- Has been treated for chronic corticoids in the past 6 months — No___ Yes___
- Has renal or liver deficiency — No___ Yes___
- Has known thrombosis or receiving treatment for blood clots — No___ Yes___
- Exhibits evidence of one of the following: asthma, cardiovascular disease (angina in chest, arrhythmia, cardiac failure, severe arterial hypertension) glaucoma or elevated intraocular pressure, diabetes, hyperlipemia — No___ Yes___
- Is older than 35 years of age and smoker (smoking a minimum 10 cigarettes per day for 2 years preceding start of study) — No___ Yes ___ / No___ Yes___
- Has known allergy to Mifepristone or Misoprostol — No___ Yes___
- Has anemia — No___ Yes___
- Is unlikely to comply with the protocol requirements or is living far away from the medical center — No___ Yes___
- Refuses to give written consent to participate — No___ Yes___

ROUSSEL HEALTH, RESEARCH AND DEVELOPMENT
PRODUCT: RU 38486
PROTOCOL # FF/92/486/24

Center #_____ Patient _____ Date of visit_____

INITIAL VISIT (DAY ONE)

DEMOGRAPHIC INFORMATION

Last name (first 3 letters) |__|__|__|

First name |__|__|__|__|__|__|__|__|

Date of birth (dd/mm/yy) |__|__/__|__/__|__|

Weight (kg) |__|__|__|.|__|

Height (cm) |__|__|__|

MEDICAL HISTORY

*Gestations (not including present pregnancy) |__|__|

Deliveries |__|__|

Other |_____| |__|__|__|__|

|_____| |__|__|__|__|

Presently receiving treatment(s) |__| no |__| yes

If YES, complete page 21, section ***"Associated treatments"***

ROUSSEL HEALTH, RESEARCH AND DEVELOPMENT
PRODUCT: RU 38486
PROTOCOL # FF/92/486/24

Center #_____ Patient #_____ Visit #

INITIAL CHECK-UP - DAY 1

CURRENT PREGNANCY

First day of last menstrual period (dd/mm/yy) |__|__/__|__/__|__|

*** Rate of Beta HCG**

Date taken (the most recent prior to D1) (dd/mm/yy) |__|__/__|__/__|__|

Value |__|__/__|__/__|__|

Units |__|__|__|__|__|__|

Has value higher than normal in absence of pregnancy |_____|

*** Ultrasound scan; gestational age at D1** |__|
(days of amenorrhea)

*** Ultrasound is obligatory in case of doubt regarding the location of pregnancy or regarding the presence of previous tubals.**

In such case, please specify:

Date of ultrasound (dd/mm/yy) |__|__/__|__/__|__|

Pregnancy confirmed |___| no |__| yes |__|

If NO, patient is excluded from study

HEMOGLOBIN RATE

To be reported on page 16.

THERAPEUTIC SCHEDULE

Dose of Mifepristone (3 units of 200mg in one dose)

Date (dd/mm/yy) |__|__/__|__/__|__|

Time (hh:mm) |__|__:|__|__|

Number of assigned dispenser containing of Mifepristone |__|__|__|__|
(also note this number on the cover page of this study)

Center # _____ Patient #_____ Visit #_____

FIRST ADMINISTRATION OF MISOPROSTOL - DAY 3

TREATMENT TOLERANCE

Did the patient experience any adverse events between the administration of Mifepristone and the administration of Misoprostol? |__| no |__| yes

* If YES, complete the following page

ADMINISTRATION OF MISOPROSTOL

First dose of Misoprostol (2 tablets in one dose)

Date (dd/mm/yy) |__|__/__|__/__|__|

Time (hh:mm) |__|__|:|__|__|

Number of the dispenser |__|__|__|__|

If Misoprostol was not administered:

- Did expulsion occur before Day 3 |__|no |__| yes |___|
- If NO, give the reason for not administering:

|_____| |___|

|_____| |___|

|_____| |___|

Center Number: 0001 Patient Number: 0003 Visit Number: 02

Tolerance of Treatment
Between Administration of Mifepristone and Misoprostol

TOLERANCE OF TREATMENT

	NO	YES	CODE	IF YES			CODE	WAS TREATMENT NECESSARY?			IF YES, COMPLETE
				MILD	MODERATE	SEVERE		NO	YES	CODE	
NAUSEA	☐1	☐2		☐1	☐2	☐3		☐1	☐2		PAGE 21 "ASSOCIATED TREATMENTS"
VOMITING	☐1	☐2		☐1	☐2	☐3		☐1	☐2		
DIARRHEA	☐1	☐2		☐1	☐2	☐3		☐1	☐2		
ADVERSE EVENTS	☐1	☐2		IF YES, COMPLETE PAGE 17 "ADVERSE EVENTS"				☐1	☐2		

Center Number: 0001 Patient Number: 0003 Visit Number: 02

Center #_____ Patient #_____ Visit #_____

OBSERVATION PERIOD AFTER FIRST ADMINISTRATION OF MISOPROSTOL - DAY 3

TREATMENT TOLERANCE

Observation at the Center is required during the 3 hours following administration of Misoprostol.

VITAL SIGNS

(one hour after the dose of Misoprostol)

Systolic blood pressure (mmHg) |__|__|__|

Diastolic blood pressure (mmHg) |__|__|__|

Heart rate (per minute) |__|__|__|

If patient is experiencing thoracic pain, irregularities in heart rate or severe hypertension, immediately perform an EKG and administer nitro-compound. Inform Roussel UCLAF at once.

CONTRACTIONS OF UTERUS

Painful uterine contractions |___| no |___|yes |__|

If YES, severity:
1 = mild 2 = moderate 3 = severe |__|

Time started (hh:mm) _____ Time stopped (hh:mm) _____

Is treatment required? |___| no |___| yes |__|

If YES, complete page 21, section ***"Associated treatments"***

Have any concomitant medications been used or changed during the study?
(not automatic, is left up to discretion of investigator before administering Misoprostol) |___| no |___|yes |__|

If YES, complete page 21, section ***"Associated treatments"***