November 20, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached a copy of an adverse event report that was recently submitted to the FDA.

Dr. Mark Nichols - patient #165

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ——— RB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 1 of 33

October 2, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA.

Dr. Creinin - patients #063, #074, #088, #104, #108, Dr. Dean - patient #147, Dr. Malloy - patients #018, #019, Dr. Westhoff - patient #116

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ——— IRB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

151

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 2 of 33

July 25, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA.

Dr. Creinin - patients #027, #033.

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ——— RB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 3 of 33

July 18, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (Protocol #166A)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA.

Dr. Dean - patient #036, Dr. Sogor - patient #012, Dr. Tyson - patients #028, #075, [redacted] - patient #071, and Dr. Creinin - patients #004, #030.

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using [redacted] RB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

[redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 4 of 33

June 2, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in inducing Abortion in pregnant Women with Amenorrhea of up to 63 Days.

Dear Dr. Poppema:

Enclosed please find a summary sheet for the Adverse Events to date in the above referenced study. In addition, we have enclosed a copy of all the Med Watch forms in chronologic order with an AE number written in the top right corner.

Please let this replace your AE section in your binder. This will be updated on a monthly basis.

If you have any questions, please feel free to contact me.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 5 of 33

SORTED BY DATE

ADE #	EVENT	SITE #	PNT #	ADVERSE EVENT
1	11/15/94	22	5	Bleed, went to Emergency Room, D&C
2	11/18/94	2	33	Nausea, vomit, dehydration, IV fluids
3	11/22/94	2	36	Patient requested D&C, bleed, IV fluids
4	11/29/94	2	27	Products Of Conception retained in cervical Os, D&C, 4 units Packed red cells
5	11/30/94	2	42	Heavy bleed, went to Emergency Room, D&C, IV fluids
6	12/10/94	1	57	Dizzy,went to Emergency Room, vacuum aspiration, IV fluids, 1unit blood
7	12/14/94	1	61	Dizzy, vacuum aspiration, IV fluids
8	12/16/94	1	62	Severe bleed, went to Emergency Room, D&C
9	12/25/94	25	15	Heavy bleed, went to Emergency Room, no treatment
10	12/27/94	25	12	Heavy bleed, went to Emergency Room, cervical Os open, vacuum aspiration
11	12/29/94	3	33	Heavy bleed, went to Emergency Room, D&C
12	12/31/94	2	70	Shooting injury - nonrelated
13	1/6/95	2	76	Bleed, went to Emergency Room, no treatment
14	1/13/95	3	50	Heavy bleed, went to Emergency Room, hypotension, D&C

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 6 of 33

15	1/14/95	25	22	Heavy bleed, faint, went to Emergency Room, D&C, IV fluids
16	1/26/95	1	107	Weak, dizzy, IV fluids
17	1/30/95	26	9	Bleed, went to Emergency Room, faint, D&C
18	2/1/95	1	114	Severe bleed, D&C, methergine
19	2/8/95	1	109	Severe bleed, went to Emergency Room, vacuum aspiration, IV fluids
20	2/8/95	1	109	Fever, hospitalized, IV antibiotics
21	2/8/95	4	37	Heavy bleed, went to Emergency Room, open cervical Os,D&C,IV fluids
22	2/9/95	1	123	Dizzy, bleed, IV fluids, methergine
23	2/12/95	3	48	Heavy bleed, went to Emergency Room, hospitalized
24	2/13/95	1	116	Chest pain, went to Emergency Room, EKG normal, patient recovered
25	2/27/95	3	76	Bleed, reported to ER bleeding had subsided, methergine
26	3/1/95	23	17	Bleed, D&C, hypotension,IV fluids,oxytocin
27	3/6/95	24	60	Heavy bleed, IV fluids, 1 unit Packed red cells
28	3/16/95	1	159	Heavy bleed, IV fluids, methergine
29	3/27/95	23	32	Vasovagal, IV fluids, oxytocin

SORTED BY DATE

30	3/29/95	23	35	Heavy bleed, IV fluids, oxytocin
31	3/29/95	23	37	Shortness of breath, D&C, IV fluids, oxytocin
32	3/31/95	26	81	Heavy bleed, fell to floor, patient recovered
33	4/1/95	23	30	Heavy bleed,D&C, IV fluids
34	4/12/95	2	158	Excess bleed, D&C, IV fluids
				ADE # is the number of the Adverse event in chronological order
				EVENT is the date of the Adverse event
				PNT # is the patient number at the specified site

Suzanne T. Poppema, M.D.
Seattle, WA
CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8
Page 8 of 33

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

by health professionals of adverse events and product problems

Page ___ of ___

Triage unit sequence # AE11

A. Patient information

1. Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
#033 In confidence	23 12/16/71	[X] female [ ] male	___ lbs or ___ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ___ (mm/dd/yy)
- [ ] life-threatening
- [ ] hospitalization – initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other: ___

3. Date of event (mm/dd/yy)

4. Date of this report (mm/dd/yy)

5. Describe event or problem

Last menstrual period 11/2/94

12/29/94: Call from patient at 10:00AM complaining of heavy bleeding for 3hrs without signs of dizziness or cramping. Advised to take methergine, 0.2mg every 4hrs and to call back if no decrease in bleeding 1hr after methergine. Call from patient's mother at 11:45 saying patient still bleeding heavily. Advised to bring patient in immediately. Call from pt's mother at 12:00 stating pt. had syncopal episode and emergency ambulance called. Call from EMT at 12:15 stating pt. BP of 80 and P 126 with heavy vaginal bleeding and pallor. EMT decision pt. too unstable to bring to office so taken to ___ (pt. member of this HMO). I spoke with ___ at ___ ER and advised him of the situation and of pt's participation in the M/M study. (See Attached)

6. Relevant tests/laboratory data, including dates

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 9 of 33

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known)
- #1 Mifepristone 600 mg
- #2 Misoprostol 400 ug

2. Dose, frequency & route used
- #1 Once PO
- #2 Once PO

3. Therapy dates (if unknown, give duration) (mm/dd/yy)
- #1 12/21/94
- #2 12/23/94

4. Diagnosis for use (indication)
- #1
- #2

5. Event abated after use stopped or dose reduced
- #1 [ ] yes [ ] no [X] doesn't apply
- #2 [ ] yes [ ] no [X] doesn't apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 [ ] yes [ ] no [ ] doesn't apply
- #2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # (for product problems only)
- - -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other: ___

5. Expiration date (mm/dd/yy)

6.
- model # ___
- catalog # ___
- serial # ___
- lot # ___
- other #

7. If implanted, give date (mm/dd/yy)

8. If explanted, give date (mm/dd/yy)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on ___ (mm/dd/yy)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA (206)546-8891

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Also reported to
- [ ] manufacturer
- [ ] user facility
- [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

...medical personnel or the product caused or contributed to the eve...

FDA Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

MIF 000709

AE11

5. Describe event or problem

(continued)

Call to ER at 16:00 patient seen and found to have postural signs of acute blood loss, heavy vaginal bleeding, and Hct of 24%. The patient underwent an emergency suction and her bleeding stopped. She was discharged from the acute care unit that evening in stable condition. Telephone follow-up on 12/30/94 found the patient stable, with no significant bleeding, and feeling fine. She never received a blood transfusion and will return as scheduled for her 2 week check. She was prescribed iron and Doxycyline.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 10 of 33

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

See OMB statement on reverse

FDA Use Only

Triage unit sequence # AE 14

A. Patient information

1. identifier	2. Age at time of event: 30 or Date of birth: 8/10/64	3. Sex	4. Weight
J		[X] female [ ] male	___ lbs or ___ kgs
In confidence			

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [X] hospitalization – initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other

3. Date of event (mo/day/yr) 1/13/95

4. Date of this report (mo/day/yr) 1/19/95

5. Describe event or problem

Last menstrual period 11/18/94
1/13/95: Telephone call from patient complaining of heavier bleeding than when here in our office, >3 pads per hour, and feeling dizzy. Advised patient to return to the clinic immediately, but because of rush hour traffic, she worried that it may take 1 1/2 - 2 hours. Because patient was feeling faint with sitting and standing, advised to go to ~~~~ ER close to home. ER physician advised. Patient arrived with severe postural hypotension. BP ~/palpable, Hct 35% and vaginal bleeding. An emergency D&C was performed with decidua and ~ removed. Post-operative Hct was 25%. Patient was sent home in the AM. No transfusion was necessary. Telephone follow-up with patient on 1/17/95 reported no significant bleeding and feels fine currently. She will return for her check-up in two weeks.

6. Relevant tests/laboratory data, including dates

Suzanne T. Poppema, M.D.
Seattle, WA --- CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 - Page 11 of 33

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Mifepristone600 mg
- #2 Misoprostol 400 ug

2. Dose, frequency & route used
- #1 Once
- #2 Once

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
- #1 1/11/95
- #2 1/13/95

4. Diagnosis for use (indication)
- #1
- #2

5. Event abated after use stopped or dose reduced
- #1 [ ] yes [ ] no [X] doesn't apply
- #2 [ ] yes [ ] no [X] doesn't apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 [ ] yes [ ] no [ ] doesn't apply
- #2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # (for product problems only)
- -
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other:

5. Expiration date (mo/day/yr)

6.
- model #
- catalog #
- serial #
- lot #
- other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Suzanne Poppema
Aurora Medical Services, Inc.
1207 N 200th Street, Suite 214
Seattle, WA 98133 (206) 546-8891

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Also reported to
- [ ] manufacturer
- [ ] user facility
- [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787
or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

MIF 000711

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only

Triage unit sequence # AE23

A. Patient information

1. Identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
48 In confidence	25	[X] female [ ] male	110 lbs or 60 kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death (mo/day/yr)
- [ ] life-threatening
- [X] hospitalization – initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [X] other: Recovered

3. Date of event (mo/day/yr): 2/12/95

4. Date of this report (mo/day/yr): 2/23/95

5. Describe event or problem

Patient contacted to schedule Visit 3 without success. On 2/12/95 patient began heavy menses, she called the emergency number and spoke with Dr. Poppema, since only bleeding 3 hours patient was told to take Ibuprofen and call back PRN. Patient instead went to ER where physician did not call Dr. Poppema. Patient had fast pulse, BP 70 mm Hg, D&C (placenta and decidua). Dr. Poppema not apprised of D&C or hospitalization until /95. Patient recovered without transfusion. ably related to both drugs.

6. Relevant tests/laboratory data, including dates

1/4/95 Hct 39%
2/12/95 Hct 29% Pre Op
2/12/95 Hct 22% Post-Op

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Gravida 1
Para 0

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 12 of 33

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Mifepristone 600 mg
- #2 Misoprostol 400 ug

2. Dose, frequency & route used
- #1 Once PO
- #2 Once PO

3. Therapy dates (if unknown, give duration) (mm/dd/yy (or best estimate))
- #1 1/4/95
- #2 1/6/95

4. Diagnosis for use (indication)
- #1 Pregnancy termination
- #2 Pregnancy Termination

5. Event abated after use stopped or dose reduced
- #1 [ ] yes [ ] no [X] doesn't apply
- #2 [ ] yes [ ] no [X] doesn't apply

6. Lot # (if known)
- #1 JMP25524-109
- #2 4H440

7. Exp. date (if known)
- #1 7/97
- #2 12/95

8. Event reappeared after reintroduction
- #1 [ ] yes [ ] no [X] doesn't apply
- #2 [ ] yes [ ] no [X] doesn't apply

9. NDC # (for product problems only) – –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other:

5. Expiration date (mo/day/yr)

6.
- model #
- catalog #
- serial #
- lot #
- other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Dr. Suzanne Poppema
Aurora Medical Service Inc.
1207 N 200th, Suite 214
Seattle, WA 98133

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Also reported to
- [ ] manufacturer
- [ ] user facility
- [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only
Triage unit sequence # AE25

A. Patient information

Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
/6	25 yrs.	[X] female [ ] male	___ lbs or ___ kgs

In confidence

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death (mo/day/yr)
- [ ] life-threatening
- [ ] hospitalization – initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [X] other: ER visit

3. Date of event (mo/day/yr): 2/27/95

4. Date of this report (mo/day/yr): 3/2/95

5. Describe event or problem

Patient went to ER 2/27/95 for bleeding and cramping (did not call service). Found on exam to have initially stopped bleeding. Hct 32 – No postural changes – ER physician called me per protocol: advised Doxycycline 100 BID x 7 days, Methergine 0.2 mg every 6 hours for 48 hours and sent home.

6. Relevant tests/laboratory data, including dates

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 13 of 33

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Mifepristone 600 mg
- #2 Misoprostol 400 ug

2. Dose, frequency & route used
- #1 Once
- #2 Once

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
- #1 2/22/95
- #2 2/24/95

4. Diagnosis for use (indication)
- #1
- #2

5. Event abated after use stopped or dose reduced
- #1 [ ] yes [ ] no [X] doesn't apply
- #2 [ ] yes [ ] no [X] doesn't apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 [ ] yes [ ] no [X] doesn't apply
- #2 [ ] yes [ ] no [X] doesn't apply

9. NDC # (for product problems only) – –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other:

5. Expiration date (mo-day-yr)

6.
- model #
- catalog #
- serial #
- lot #
- other #

7. If implanted, give date (mo-day-yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Dr. Suzanne Poppema
Aurora Medical Service, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Also reported to
- [ ] manufacturer
- [ ] user facility
- [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

MIF 000713

April 26, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (166A)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA.
Dr. ——— - patients #30, #32, #35, and #37, Dr. Sheehan - patient #81,
Dr. Haskell - patient #158, and Dr. Mishell - patient #159.

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ——— RB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

157

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 14 of 33

March 6, 1995

[redacted]

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (#166A/B)

Dear ———

Please be advised of the Serious Adverse Events that have occurred during this study since our last report to you (2/17/95). These events were reported to the FDA. In adhering with the FDA regulations, all —— study sites who are actively participating in this trial have been notified. (Drs. Haskell, Poppema, Sheehan, Tyson, Vargas)

Enclosed, please find the letter sent to each investigator along with the Adverse Event Reports. We are notifying you, as the IRB responsible for these centers of these events. Dr. Poppema - patients #048 and #076.

Sincerely,

[redacted]

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 15 of 33

March 6, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (#166A/B)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA. (Dr. Poppema - patients #048 and #076)

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ——— IRB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 16 of 33

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

Form Approved: OMB No. 0910-0291 Expires: 12/31/
See OMB statement on reverse

FDA Use Only

Triage unit sequence #

Patient information

Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
076 In confidence		[X] female [ ] male	___ lbs or ___ kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ___ (mo/day/yr)
- [ ] life-threatening
- [ ] hospitalization – initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [X] other: ER visit

3. Date of event (mo/day/yr): 2/27/95

4. Date of this report (mo/day/yr): 3/2/95

5. Describe event or problem

Patient went to ER 2/27/95 for bleeding and cramping (did not call AMS service). Found on exam to have initially stopped bleeding. Hct 32 - No postural changes - ER physician called me per protocol: advised Doxycycline 100 BID x 7 days, Methergine 0.2 mg every 6 hours for 48 hours and sent home.

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 17 of 33

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Mifepristone 600 mg
- #2 Misoprostol 400 ug

2. Dose, frequency & route used
- #1 Once
- #2 Once

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
- #1 2/22/95
- #2 2/24/95

4. Diagnosis for use (indication)
- #1
- #2

5. Event abated after use stopped or dose reduced
- #1 [ ] yes [ ] no [X] does not apply
- #2 [ ] yes [ ] no [X] does not apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 [ ] yes [ ] no [X] does not apply
- #2 [ ] yes [ ] no [X] does not apply

9. NDC # (for product problems only)
- -
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other:

5. Expiration date (mo/day/yr)

6.
- model #
- catalog #
- serial #
- lot #
- other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Dr. Suzanne Poppema
Aurora Medical Service, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Also reported to
- [ ] manufacturer
- [ ] user facility
- [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the eve

MIF 000717

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

Form Approved: OMB No. 0910-0291 Expires 12/31
See OMB statement on reverse

FDA Use Only

Triage unit sequence #

A. Patient information

Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
48 In confidence	25	[X] female [ ] male	110 lbs or 60 kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ___ (mo/day/yr)
- [ ] life-threatening
- [X] hospitalization – initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [X] other: Recovered

3. Date of event (mo/day/yr): 2/12/95

4. Date of this report (mo/day/yr): 2/23/95

5. Describe event or problem

Patient contacted to schedule Visit 3 without success. On 2/12/95 patient began heavy menses, she called the emergency number and spoke with Dr. Poppema, since only bleeding 3 hours patient was told to take Ibuprofen and call back PRN. Patient instead went to ER where physician did not call Dr. Poppema. Patient had fast pulse, BP 70 mm Hg, D&C (placenta and decidua). Dr. Poppema not apprised of D&C or hospitalization until 2/21/95. Patient recovered without transfusion. Probably related to both drugs.

6. Relevant tests/laboratory data, including dates

1/4/95 Hct 39%
2/12/95 Hct 29% Pre Op
2/12/95 Hct 22% Post Op

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Gravida 1
Para 0

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 18 of 33

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Mifepristone 600 mg
- #2 Misoprostol 400 ug

2. Dose, frequency & route used
- #1 Once PO
- #2 Once PO

3. Therapy dates (if unknown, give duration) (from/to or best estimate)
- #1 1/4/95
- #2 1/6/95

4. Diagnosis for use (indication)
- #1 Pregnancy termination
- #2 Pregnancy Termination

5. Event abated after use stopped or dose reduced
- #1 [ ] yes [ ] no [X] does not apply
- #2 [ ] yes [ ] no [X] does not apply

6. Lot # (if known)
- #1 JMP25524-109
- #2 4H440

7. Exp. date (if known)
- #1 7/97
- #2 12/95

8. Event reappeared after reintroduction
- #1 [ ] yes [ ] no [X] does not apply
- #2 [ ] yes [ ] no [X] does not apply

9. NDC # (for product problems only) - -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other:

5. Expiration date (mo/day/yr)

6.
- model #
- catalog #
- serial #
- lot #
- other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Dr. Suzanne Poppema
Aurora Medical Service Inc.
1207 N 200th, Suite 214
Seattle, WA 98133

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Also reported to
- [ ] manufacturer
- [ ] user facility
- [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the eve

MIF 000718

INSTITUTIONAL REVIEW BOARD

January 24, 1995

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

Please be advised that the Institutional Review Board under the auspices of ——— ——— is in receipt of the Adverse Event Reports for the study entitled, "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days (Protocol #166 A/B)".

The IRB has received the following patients' Medwatch Forms:

Investigator	Patient #
Dr. Nichols	12
	15
	22
Dr. Poppema	33
	50
Dr. Haskell	76
Dr. Mishell	61
	Patient I.D. ———

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99 ———
Exhibit 8 Page 19 of 33

The Medwatch Forms and any available reports were sent to you by _____ While Dr. Nichols and Dr. Mishell are not utilizing this IRB, any serious adverse events requiring notification to FDA must be reported to all participating investigators and their IRBs. Please insure that you maintain these reports in compliance with federal regulations.

The IRB is aware of these adverse events and has not determined any increased risk to the patient or a change in the risk to benefit ratio. These side effects have been reported in previous clinical trials of the combination of drugs and ongoing safety evaluation is being maintained.

Sincerely,

/S/

January 23, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (#166A/B)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA. (Dr. Nichols - patient #022 and Dr. Poppema - patient #050)

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ———— IRB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

S

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 21 of 33

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___

Form Approved OMB No. 0910-0291 Expires 12/31/98
See OMB statement on reverse.

FDA Use Only
Triage unit sequence #

A. Patient information

1. Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
u50	30 / 8/10/64	[X] female [ ] male	___ lbs or ___ kgs

In confidence

B. Adverse event or product problem

1 [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2 Outcomes attributed to adverse event (check all that apply)
- [ ] death
- [ ] life-threatening
- [X] hospitalization - initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other

3 Date of event (mo/day/yr) 1/13/95

4 Date of this report (mo/day/yr) 1/19/95

5. Describe event or problem

Last menstrual period 11/18/94
1/13/95: Telephone call from patient complaining of heavier bleeding than when here in our office, >3 pads per hour, and feeling dizzy. Advised patient to return to the clinic immediately, but because of rush hour traffic, she worried that it may take 1 1/2 - 2 hours. Because patient was feeling faint with sitting and standing, advised to go to ———— ER close to home. ER physician advised. Patient arrived with severe postural hypotension. BP [illegible]/palpable, Hct 35% and vaginal bleeding. An emergency D&C was performed with decidua and [illegible] removed. Post-operative Hct was 25%. Patient was sent home in the AM. No transfusion was necessary. Telephone follow-up with patient on 1/17/95 reported no significant bleeding and feels fine currently. She will return for her check-up in two weeks.

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 22 of 33

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Mifepristone600 mg
- #2 Misoprostol 400 ug

2. Dose, frequency & route used
- #1 Once
- #2 Once

3. Therapy dates (if unknown, give duration) (mo/day/yr or best estimate)
- #1 1/11/95
- #2 1/13/95

4. Diagnosis for use (indication)
- #1
- #2

5. Event abated after use stopped or dose reduced
- #1 [ ] yes [ ] no [X] doesn't apply
- #2 [ ] yes [ ] no [X] doesn't apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 [ ] yes [ ] no [ ] doesn't apply
- #2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # (for product problems only)
- -
- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other:

5. Expiration date (mo/day/yr)

6.
- model #
- catalog #
- serial #
- lot #
- other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Suzanne Poppema
Aurora Medical Services, Inc.
1207 N 200th Street, Suite 214
Seattle, WA 98133 (206) 546-8891

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Also reported to
- [ ] manufacturer
- [ ] user facility
- [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. [ ]

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

MIF 000722

January 18, 1995

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (#166A/B)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA. (Dr. Nichols - patients #012 & 015, Dr. Mishell - patient #061, Dr. Haskell - patient #076 and Dr. Poppema - patient #033)

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ——— RB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 23 of 33

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

by health professionals of adverse events and product problems

Page ___ of ___

Triage unit sequence #

Patient information

Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
#033	23	[X] female [ ] male	___ lbs or ___ kgs
In confidence	12/16/71		

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- [ ] death ___ (mo/day/yr)
- [ ] life-threatening
- [ ] hospitalization – initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other: ___

3. Date of event (mo/day/yr) ___

4. Date of this report (mo/day/yr) ___

5. Describe event or problem

Last menstrual period 11/2/94

12/29/94: Call from patient at 10:00AM complaining of heavy bleeding for 3hrs without signs of dizziness or cramping. Advised to take methergine, 0.2mg every 4hrs and to call back if no decrease in bleeding 1hr after methergine. Call from patient's mother at 11:45 saying patient still bleeding heavily. Advised to bring patient in immediately. Call from pt's mother at 12:00 stating pt. had syncopal episode and emergency ambulance called. Call from EMT at 12:15 stating pt. BP of 80 and P 126 with heavy vaginal bleeding and pallor. EMT decision pt. too unstable to bring to office so taken to _____ (pt. member of this HMO). I spoke with _____ ER and advised him of the situation and of pt's participation in the M/M study. (See Attached)

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 24 of 33

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 Mifepristone 600 mg
- #2 Misoprostol 400 ug

2. Dose, frequency & route used
- #1 Once PO
- #2 Once PO

3. Therapy dates (if unknown, give duration) (mo/day/yr or best estimate)
- #1 12/21/94
- #2 12/23/94

4. Diagnosis for use (indication)
- #1
- #2

5. Event abated after use stopped or dose reduced
- #1 [ ] yes [ ] no [X] doesn't apply
- #2 [ ] yes [ ] no [X] doesn't apply

6. Lot # (if known)
- #1
- #2

7. Exp. date (if known)
- #1
- #2

8. Event reappeared after reintroduction
- #1 [ ] yes [ ] no [ ] doesn't apply
- #2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # (for product problems only)
- - -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other: ___

5. Expiration date (mo/day/yr)

6.
- model # ___
- catalog # ___
- serial # ___
- lot # ___
- other # ___

7. If implanted, give d. (mo/day/yr)

8. If explanted, give d (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA (206)546-8891

2. Health professional? [X] yes [ ] no

3. Occupation: Physician

4. Also reported to
- [ ] manufacturer
- [ ] user facility
- [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. [ ]

FDA

Mail to: MEDWATCH · 5600 Fishers Lane · Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the ev

MIF 000724

5. Describe event or problem

(continued)

Call to ER at 16:00 patient seen and found to have postural signs of acute blood loss, heavy vaginal bleeding, and Hct of 24%. The patient underwent an emergency suction and her bleeding stopped. She was discharged from the acute care unit that evening in stable condition. Telephone follow-up on 12/30/94 found the patient stable, with no significant bleeding, and feeling fine. She never received a blood transfusion and will return as scheduled for her 2 week check. She was prescribed iron and Doxycyline.

Aurora Medical Services Inc. PS

1207 North 200th Street Suite 214

Seattle Washington 98133

(206) 546-8891

FAX 546-9641

January 3, 1995

Irving Spitz, M.D.
The Population Council
1230 York Avenue
New York, New York, 10021

Dear Dr. Spitz,

Adverse event report: Pt initials ——J33
DOB: 12/16/71
LMP: 11/2/94 Final assessment of amennorhea: 52 days, Group 2
Hct on 12/21/94: 39%
mifepristone admin: 12/21/94 @ 10:45 600mg.
Misoprostol admin: 12/23/94 @ 09:00 400 mg.
U/S p4hrs : no sac seen but blood and tissue still in uterus.

12/29/94: Call from pt @10:00 AM c/o heavy bleeding for 3 hrs without sx of dizziness or cramping. Advised to take methergine, 0.2mg q 4hrs and to call back if no decrease in bleeding 1hr after methergine. Call from pt's mother @11:45 saying pt still bleeding heavily; advised to bring pt in immediately. Call from pt's mother @12:00 stating pt had syncopal episode and emergency ambulance called. Call from EMT @12:15 stating pt BP of 80 and P 126 with heavy vaginal bleeding and pallor. EMT decision pt too unstable to bring to office so taken to ER(pt member of this HMO).

I spoke with ———————— ER and advised him of the situation and of pt's participation in the M/M study.

Call to ER @ 16:00 pt seen and found to have postural signs of acute blood loss, heavy vaginal bleeding, and Hct of 24%. The patient underwent an emergency suction and her bleeding stopped. She was discharged from the acute care unit that evening in stable condition. Telephone follow/up on 12/30/94 found the patient stable, with no significant bleeding, and feeling fine. She never received a blood transfusion and will return as scheduled for her 2 week check. She was prescribed iron and Doxycycline.

Principal Investigator:
Suzanne Poppema, MD

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 26 of 33

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

by health professionals of adverse events and product problems

Page ___ of ___

Triage unit sequence #

Patient information

Patient identifier	2. Age at time of event: or Date of birth:	3. Sex	4. Weight
#033 In confidence	23 12/16/71	[X] female [ ] male	___ lbs or ___ kgs

B. Adverse event or product problem

1 [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2 Outcomes attributed to adverse event (check all that apply)

- [ ] death (mo/day/yr)
- [ ] life-threatening
- [ ] hospitalization – initial or prolonged
- [ ] disability
- [ ] congenital anomaly
- [ ] required intervention to prevent permanent impairment/damage
- [ ] other:

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem Last menstrual period 11/2/94

12/29/94: Call from patient at 10:00AM complaining of heavy bleeding for 3hrs without signs of dizziness or cramping. Advised to take methergine, 0.2mg every 4hrs and to call back if no decrease in bleeding 1hr after methergine. Call from patient's mother at 11:45 saying patient still bleeding heavily. Advised to bring patient in immediately. Call from pt's mother at 12:00 stating pt. had syncopal episode and emergency ambulance called. Call from EMT at 12:15 stating pt. BP of 80 and P 126 with heavy vaginal bleeding and pallor. EMT decision pt. too unstable to bring to office so taken to _____ pt. member of this HMO). I spoke with _____ & and advised him of the situation and of pt's participation in the M/M study. (See Attached)

6. Relevant tests/laboratory data, including dates

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 27 of 33

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Mifepristone 600 mg

#2 Misoprostol 400 ug

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) (mo/day/yr or best estimate)
#1 Once PO	#1 12/21/94
#2 Once PO	#2 12/23/94

4. Diagnosis for use (indication)

#1

#2

5. Event abated after use stopped or dose reduced

#1 [ ] yes [ ] no [X] doesn't apply

#2 [ ] yes [ ] no [X] doesn't apply

6. Lot # (if known)

#1

#2

7. Exp. date (if known)

#1

#2

8. Event reappeared after reintroduction

#1 [ ] yes [ ] no [ ] doesn't apply

#2 [ ] yes [ ] no [ ] doesn't apply

9. NDC # (for product problems only)

- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
- [ ] health professional
- [ ] lay user/patient
- [ ] other:

5. Expiration date (mo/day/yr)

6.
model # ___
catalog # ___
serial # ___
lot # ___
other # ___

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
[ ] yes [ ] no [ ] returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

Dr. Suzanne Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA (206)546-8891

2. Health professional?	3. Occupation	4. Also reported to
[X] yes [ ] no	Physician	[ ] manufacturer [ ] user facility [ ] distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box. [ ]

FDA

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

FDA Form 3500 (6/93) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

MIF 000727

5. Describe event or problem

(continued)

Call to ER at 16:00 patient seen and found to have postural signs of acute blood loss, heavy vaginal bleeding, and Hct of 24%. The patient underwent an emergency suction and her bleeding stopped. She was discharged from the acute care unit that evening in stable condition. Telephone follow-up on 12/30/94 found the patient stable, with no significant bleeding, and feeling fine. She never received a blood transfusion and will return as scheduled for her 2 week check. She was prescribed iron and Doxycyline.

December 23, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days" (#166A/B)

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached a copy of an adverse event report that was recently submitted to the FDA.

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study. For those centers using ——— IRB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 29 of 33

INSTITUTIONAL REVIEW BOARD

December 14, 1994

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

Please be advised that the Institutional Review Board under the auspices of ———— is in receipt of the five (5) Adverse Event Reports for the study entitled, "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days (Protocol #166 A/B)".

The IRB has the following patients' Medwatch Forms:

Investigator	Patient #
Dr. Vargas	#005
Dr. Haskell	#027
	#033
	#036
	#042

The Medwatch Forms and any available reports were sent to you by ————, ———— on November 23, 1994 (for patient #005) and on December 6, 1994 (the four patients from Dr. Haskell's site). Please insure that you maintain these reports in compliance with federal regulations.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 30 of 33

The IRB is aware of these adverse events and has not determined any increased risk to the patient or a change in the risk to benefit ratio. These side effects have been reported in previous clinical trials of the combination of drugs and ongoing safety evaluation is being maintained.

Sincerely.

151

December 5, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: Protocol 166A/B

Dear Dr. Poppema:

To assure that all investigators are kept current on safety issues and to comply with all applicable regulations of the FDA, please find attached copies of adverse event reports that were recently submitted to the FDA.

Please forward a copy of this report to your IRB and place a copy in your clinical trial binder for this study.

For those centers using [redacted] IRB, this submission will be taken care of.

Should you have any questions, please contact me directly.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 32 of 33

November, 23, 1994

Dr. Suzanne T. Poppema
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Re: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of up to 63 Days"

Dear Dr. Poppema:

On November 15, 1994 a patient enrolled in the Mifepristone/Misoprostol study experienced a serious adverse event which required hospitalization of the patient.

The patient is 26 years of age, Gravida IV, para III with three living children. She has a history post-partum hemorrhage with the second pregnancy. She was at 63 days gestation upon study enrollment.

On November 12, 1994 the patient received the study dose of misoprostol. She was stable throughout the four hour observation period. On the morning of the 15th the subject experienced an episode of very heavy bleeding. She was transported to a local hospital. Examination revealed that the cervical os was open and POC were visible at the os, detached and lodged in the lower uterine segment. Suction curettage was performed and the bleeding stabilized. Post-operative Hgb was 5.6 Gm% and the patient was admitted for overnight observation. On the morning of the 16th the patient's Hgb remained at 5.6 Gm% and she was symptomatic. Two units of packed red cells were infused over a six hour period. The patient was discharged late on the 16th.

Please forward a copy of this report to your IRB and place a copy in your Clinical Trial Binder for the above referenced study. Centers utilizing the IRB under the auspices of ——— ——— will have a copy submitted to the IRB for them.

If you have any questions please contact ——— . the Population Council or me.

Sincerely,

/S/

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 8 Page 33 of 33

October 13, 1994

CONFIDENTIAL

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 A

SPONSOR: The Population Council, Inc.
1230 York Avenue
New York, New York 10021

CONFIDENTIAL AND PROPRIETARY

Signature, Principal Investigator

APPROVED BY
IRB
OCT 27 1994

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 11 Page 1 of 38

TABLE OF CONTENTS

1. INTRODUCTION

Mifepristone is a synthetic steroid currently used for medical abortion in France, Sweden, United Kingdom and China. It acts as a competitive blocker of progesterone and cortisol through binding to their receptors. Because of its antiprogesterone activity, mifepristone has been developed primarily as a medical abortifacient. When used alone in different regimens with total doses ranging from 140 to 1600 mg administered over one to ten days, the success rate of abortion in women with amenorrhea of less than 50 days duration usually varied between 64-85%[1].

Subsequent studies demonstrated that when mifepristone (600 mg) was followed two days later by a prostaglandin analog administered either by the intramuscular route (sulprostone, a prostaglandin E_2 analog), or as a vaginal pessary (gemeprost, a prostaglandin E_1 analog), the efficacy rate for complete abortion increased to 95% and above. Based on these observations, mifepristone has been marketed in France since September 1989 as a medical alternative to surgical abortion for the termination of pregnancies in women with amenorrhea of 49 days or less. Recently, this mifepristone - prostaglandin regimen was approved in the United Kingdom, and in Sweden. In the latter two countries, this combination is used in women with amenorrhea of up to 63 days.

In Europe there is now an accumulated experience with over 150,000 subjects who have received mifepristone together with various prostaglandins. Clinical trials have been conducted in several countries and have confirmed the initial experience. Unlike treatment with mifepristone alone where the success rate decreased with advancing duration of amenorrhea, the combination was effective up to 63 days of amenorrhea and in various published studies, the incidence of abortion induction ranged from 92.7% to 99%[1].

The most comprehensive study published to date comprises 16,369 subjects from over 450 clinics[2]. In this study 0.8% of the cases experienced uterine bleeding significant enough to necessitate vacuum aspiration or dilatation and curettage and in 0.07% (11 women), a blood transfusion was required. Significant cardiovascular side effects were reported in four cases following sulprostone administration. In three of these subjects, there was severe hypotension necessitating infusion of macromolecular solutes and in the final subject, a 38 year-old smoker, there was an acute myocardial infarction. In these four subjects, symptoms commenced within one hour of sulprostone administration and all recovered uneventfully. However, in general use, there was a fatal myocardial infarction in one woman, who was a 31-year-old heavy smoker, following sulprostone[3]. No cardiovascular complications have been reported following gemeprost, but this may be related to the fact that this analog has been used less often than sulprostone. Sulprostone is rapidly absorbed into the circulation following intramuscular injection, therefore, it is not unreasonable to assume that this prostaglandin carries a higher risk of cardiovascular problems than preparations that are administered orally or vaginally and are absorbed more gradually. Moreover, gemeprost, unlike sulprostone, is an E_1 analog.

As a consequence, parenteral prostaglandins should be used cautiously in women with heart disease, those over 35 years of age or in heavy smokers. The French health authorities have in fact withdrawn sulprostone as one of the prostaglandin preparations which can be given with mifepristone.

APPEARS THIS WAY
ON ORIGINAL

Because of the cardiovascular side effects reported with sulprostone as well as the inconvenience of both sulprostone and gemeprost which both require refrigeration, alternate prostaglandin preparations are now being used. Misoprostol, (methyl 11α, 16-dihydroxy-16-methyl-9-oxoprost-13 E-en-1-oate) is a prostaglandin E_1 analog that has been safely used for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers in patients at high risk for complications from gastric ulcers for many years; for this indication, it is given in an oral dose of 200 μg four times daily. Its effects on uterine tone are similar to those of other prostaglandins. Misoprostol is inexpensive, orally active and stable. In a recently published French study in women with amenorrhea of 49 days or less, one group comprising 505 women received 400 μg misoprostol 48 hours after mifepristone; the success rate for termination of pregnancy was 96.9%[4]. A second group of 390 women initially followed the same protocol, but if pregnancy was not terminated within four hours after misoprostol, the women were offered an additional 200 μg dose of misoprostol. In this second group, the overall success rate was 98.7%. These results indicate that the combination of mifepristone and misoprostol is of equal or greater effectiveness than the combination of mifepristone and either parenteral or vaginal prostaglandin for the termination of early pregnancy.[4] No serious cardiovascular side effects have been observed. Other side effects were neither more frequent nor more severe than after parenteral or vaginal prostaglandin preparations[4].

A study from Britain reported complete abortion in 92 out of 99 women with amenorrhea of less than 57 days who were given 200 mg mifepristone followed 48 hours later by 600 μg misoprostol. There were three on-going pregnancies and four incomplete abortions. Vomiting was exhibited in 24% and diarrhea in 7% of the women. No analgesia was needed in 62% of the women[5].

In the two studies reported above, approximately 60-80% of women aborted during the four hours following prostaglandin administration. A number of side effects have been observed during this four hour period. These include: uterine pain, nausea, vomiting and diarrhea. In one of these studies the incidence of nausea, vomiting and diarrhea were 43%, 17% and 14% respectively[4]. It is for these reasons that it is recommended that women be monitored in the clinic for four hours following prostaglandin administration.

In Europe, over 52,000 women have received mifepristone followed 48 hours later by misoprostol without serious heart complications.

2. SUMMARY OF STUDY

The aim of the study is to determine the safety, efficacy, acceptability and feasibility of mifepristone plus misoprostol in inducing abortion, within the U.S. health care system setting, when administered to women exhibiting amenorrhea of varying duration (up to 63 days). **The duration of amenorrhea will be defined throughout this document as the number of days from the first day of the last menstrual period.** In addition to the large pivotal studies, a small initial pilot study will be conducted to enable the investigators to gain first hand experience with the proposed dosing regimen.

A total of 1,050 pregnant subjects will be enrolled in this and an identical sister protocol, to be conducted simultaneously. Thus a total of 2,100 subjects will be enrolled in the two trials. Three groups of subjects will be examined:

Group 1: Amenorrhea of $\leq$ 49 days
Group 2: Amenorrhea of 50 through 56 days
Group 3: Amenorrhea of 57 through 63 days

Analysis will also be conducted on safety, efficacy and acceptability of all subjects taken as a single group, regardless of the duration of amenorrhea. This will be a multicenter trial utilizing a minimum of six centers in each of the two studies. The centers will all perform pregnancy interruption on a regular basis. The centers will have access to facilities for blood transfusion and routine emergency resuscitation techniques. In all the trial centers, the recruitment of subjects will be such that, as closely as possible, equal numbers of subjects will be enrolled into each of the three groups defined above.

Subjects shall visit the study center three times, unless state law requires an additional, initial informational visit with a mandatory waiting period before the process can begin. At the initial visit (Day 1; after any required statutory waiting period), a full history and physical examination will be performed and the duration of amenorrhea will be determined and the reasons for selecting a medical abortion will all be recorded. At this visit, 600 mg of mifepristone (three 200 mg tablets) will be administered. The subject will return to the study center for the second visit on Day 3 to receive oral misoprostol (400 μg as two 200 μg tablets). The subject will be monitored at the center for at least four hours post the administration of the prostaglandin. The third visit will occur on Day 15. At this visit the completeness of the medical pregnancy termination will be assessed. In the event that the pregnancy is on-going at this time, or if the abortion has been incomplete, either vacuum aspiration or dilation and curettage will be performed. Subjects who undergo a surgical abortion at any time during their enrollment in the study will return to the center two weeks post the surgical procedure for a follow-up assessment.

3. OBJECTIVE

The objective of this trial is to evaluate the effectiveness, safety, acceptability and feasibility of mifepristone plus misoprostol in inducing abortion when given to women, who have experienced up to 63 days of amenorrhea, within the U.S. health care system setting. Prior to initiation of the pivotal studies, a pilot study comprising 15 women will be performed at each of the selected study centers. The purpose of this pilot trial is to give the investigators exposure to the proposed dosing regimen so they will have first hand experience prior to the initiation of the pivotal studies. The results of the pilot trial will be included in the safety analysis for the product, but the efficacy data will be treated as a subgroup analysis relative to the pivotal trials.

Investigators selected to conduct the trials will be experienced abortion providers and medical investigators. They should have access to an IRB able to review the protocol, and will have malpractice insurance as well as general liability insurance for the clinic, hospital or office where the study will be performed. The investigators should be able to complete the study in six months at a maximum.

The investigators will operate in an appropriate study center; the study center will:

a) Provide routine emergency resuscitation such as O_2, Ambu bag and will be staffed with personnel trained in routine emergency care.

b) Have access on a 24 hour a day basis to blood transfusion, D & C and more elaborate resuscitation procedures.

c) Have space to conduct the study including a room where a woman can be monitored for at least four hours after the prostaglandin administration.

d) Have the physician responsible for the study on call on a 24 hour a day basis, or his/her delegate of equal qualification.

e) Have adequate and sufficient trained personnel for counselling of subjects and conduct of the study.

f) Have transvaginal ultrasound available and personnel trained in the use of the equipment as well as the interpretation of the sonograms for the assessment of gestational age in relation to the reported duration of amenorrhea.

g) Investigators and staff will answer a provided questionnaire at the completion of the study.

4. PATIENT SELECTION

4.1 Patient Sample:

4.1.1 Number of patients: A total of 1,050 patients per each of the identical trials for a total of 2,100 subjects will be enrolled at multiple centers.

4.1.2 Age range: 18 years or older.

4.1.3 Residents of the United States.

4.2 Inclusion Criteria:

4.2.1 Good general health.

4.2.2 Age 18 years or older.

4.2.3 Request termination of pregnancy.

4.2.4 Agree to undergo surgical pregnancy termination in case of failure of the medical abortion method being evaluated.

4.2.5 Have an intrauterine pregnancy of known duration which is less than or equal to 63 days of amenorrhea period. The final determined estimated duration of pregnancy should be less than 64 days of amenorrhea, and as confirmed by uterine size on pelvic examination and ultrasonographic examination.

4.2.6 Have a positive urine pregnancy test.

4.2.7 Willing and able to participate in the study after its precise nature and duration have been explained.

4.2.8 Able and willing to sign an informed consent form.

4.2.9 Resident of the United States.

4.3 Exclusion Criteria:

4.3.1 Evidence of the presence of any disorder which represents a contraindication to the use of mifepristone (e.g., chronic corticosteroid administration, adrenal disease) or misoprostol (e.g., asthma, glaucoma, mitral stenosis, arterial hypotension, sickle cell anemia, or known allergy to prostaglandin).

4.3.2 History of severe liver, respiratory, or renal disease or thromboembolism.

4.3.3 Cardiovascular disease (e.g., angina, valve disease, arrythmia, cardiac failure).

4.3.4 Hypertension being treated on a chronic basis or untreated patients who present with: a blood pressure of > 140 (systolic) or > 90 (diastolic).

4.3.5 Anemia (hemoglobin level below 10 g/dL or hematocrit below 30%) at the Day 1 visit.

4.3.6 A known clotting defect or receiving anticoagulants.

4.3.7 Subjects with an IUD in place.

4.3.8 Insulin dependent diabetes mellitus.

4.3.9 More than 63 days of amenorrhea or results of bimanual pelvic examination or vaginal ultrasound which are inconsistent with 63 days or less of amenorrhea.

4.3.10 Breast-feeding.

4.3.11 Adnexal masses or adnexal tenderness on pelvic examination suggesting pelvic inflammatory disease.

4.3.12 Ectopic pregnancy or threatened abortion.

4.3.13 Women 35 years of age or older who smoke more than 10 cigarettes per day and have another risk factor for cardiovascular disease (e.g., diabetes mellitus, hyperlipidemia, hypertension or family history of ischemic heart diseases).

4.3.14 Unlikely to understand or comply with the protocol requirements.

4.3.15 Women who cannot reach the source of emergency medical care that serves the abortion center within one (1) hour from (a) their home or place of work and (b) the abortion center.

5. STUDY MEDICATION

5.1 Assignment of Study Medication

This is a multicenter trial evaluating the effectiveness, safety and acceptability of mifepristone plus misoprostol in inducing abortion when given to women in one of three groups depending upon the duration of amenorrhea. The three groups are:

Group 1 - Amenorrhea of $\leq$ 49 days
Group 2 - Amenorrhea of 50 through 56 days
Group 3 - Amenorrhea of 57 through 63 days

As closely as is possible, equal numbers of subjects will be enrolled into each of the three groups. There may be differing numbers of patients enrolled from center to center, but the number per group per center should be approximately one third into each of the groups.

5.2 Dosage and Administration

There will be three visits to the study center. At the initial visit (Day 1), a full history and physical examination will be performed and the duration of amenorrhea will be determined and the reasons for selecting a medical abortion will all be recorded. At this visit, 600 mg of mifepristone (three 200 mg tablets) will be administered orally. The subject will return to the study center for the second visit on Day 3 to receive oral misoprostol (400 μg as two 200 μg tablets). The subject will be monitored at the center for at least four hours post the administration of the prostaglandin. The third visit will occur on Day 15. At this visit the completeness of the medical pregnancy termination will be assessed and an acceptability questionnaire administered. In the event that the pregnancy is on-going at this time, or if the abortion has been incomplete, either vacuum aspiration or dilation and curettage will be performed. Subjects who undergo a surgical abortion at any time during their enrollment in the study will return to the center two weeks post the surgical procedure for a follow-up assessment.

5.3 Packaging

A) Mifepristone — Mifepristone will be provided as 200 mg tablets of micronized mifepristone.

B) Misoprostol — Misoprostol will be obtained locally by each investigator as 200 μg tablets of commercially available misoprostol.

All study supplies will be kept in a locked, dry cabinet.

5.4 Labeling

A) Mifepristone — Mifepristone will have a label which will include product identification, expiration date, and drug dose. In addition the following will be printed on the labels: CAUTION: New drug. Limited by Federal Law to Investigational Use. All medication packets will be labelled with the protocol number.

B) Misoprostol — Misoprostol will be obtained locally by each investigator as 200 μg tablets of commercially available misoprostol and dispensed from the center pharmacy.

5.5 Concomitant Medications

No salicylates, indomethacin, or any other drug which inhibits prostaglandin synthesis should be taken. If necessary, analgesics belonging to other pharmacologic classes or spasmolytic drugs may be used. Drugs such as trifluoperazine and related phenothiazines (for treatment of nausea and vomiting) that could increase the risk of hypotension must be avoided as should oxytocin and any other prostaglandin preparation.

The use of concomitant medications during the course of this study will be recorded in the Case Report Form, and these data will be analyzed.

6. STUDY PROCEDURES

Each participating study center will record on a daily basis the number of subjects recruited in each of the three groups. All women approached to participate in the study will be recorded in the study data. Those who refuse to participate in the trial will have a special form completed for the database. These data will be communicated to the sponsor on a weekly basis. At each center, the number of subjects recruited into each of the groups will be equal to one-third the total assigned to the center if possible. When any of the groups has been filled, no further recruitment into that particular group will be conducted. Under no circumstances will any member of the study center staff suggest that a subject appearing at the center, with a duration of amenorrhea consistent with a completed group, be deferred in her request for pregnancy termination to allow for enrollment into an open group at a later time.

6.1 VISIT 1 (Admission, Day 1 of Study)

At the time of the subjects enrollment (Day 1), all the following should be done:

- Counseling.

- Medical, obstetrical and gynecological history.

- Medical examination, including: height, weight, blood pressure, and pulse.

- Bimanual pelvic examination.

- Urine pregnancy test.

- Quantitative Serum ßhCG.

- Vaginal ultrasound.

- Determination of Rh status and where routinely collected, the blood group.

- Hemoglobin or hematocrit determination.

Food should be withheld for one hour prior to and one hour post administration of the study drug. At admission to the study, the three tablets of mifepristone (600 mg total) will be swallowed by the subject with no more than 240 mL of water in the presence of a member of the center's study staff who will record the date and time of the administration.

Subjects who smoke will be instructed to refrain from smoking until after the administration of misoprostol at Visit 2, and an appointment will be made for Visit 2.

Subjects will be given a copy of the informed consent and patient diary card describing symptoms which require emergency treatment. These include: heavy bleeding, fever, and severe abdominal pain. The subjects will be given the address and 24 hour telephone number of a medical center (including the name of physicians) which cares for patients on a 24 hour a day basis.

A diary will be provided to each of the subjects for recording medications and symptoms, such as pain, nausea, vomiting and diarrhea. The diary will also be used to record the occurrence of vaginal bleeding on each day. The subject will be instructed to record the bleeding relative to their normal menstrual flow (e.g., lighter, the same as or heavier than normal). If the expulsion takes place before Visit 2, the date and time should be recorded on the subjects diary.

6.2 VISIT 2 (Prostaglandin Administration, Day 3 of Study)

Visit 2 will be conducted on Day three (3) of the study. The following will be performed:

- Clinical examination.

- If the patient believes that expulsion occurred prior to Visit 2, the date and time will be recorded on the case report form as they were noted in the subjects diary. Since it is difficult to confirm that an abortion at this time is complete, nearly all subjects will require misoprostol. If however, the physician can verify unequivocally that complete abortion has occurred, the misoprostol will not be administered. If the abortion is incomplete or if there is any uncertainty about the completeness of the abortion, the misoprostol will be administered.

- Brief interview and review of the diary.

- Any adverse events which occurred since Visit 1 will be recorded on the case report form.

- Subject will receive an injection of anti-D globulin if the subject is Rh negative, if indicated.

- Food should be withheld for one hour prior to and one hour post the administration of misoprostol. The two tablets of misoprostol (400 μg total) will be swallowed by the subject with no more than 240 mL of water in the presence of a member of the center's study staff who will record the date and time of the administration.
- The subject will be observed at the study center for the four hour period post the administration of misoprostol at a minimum. The facility should be capable of surgical termination of pregnancy (by vacuum aspiration or dilation and curettage) and have access to blood transfusion and emergency resuscitation.

- During the observation period, the following should be recorded at least hourly:

  - Occurrence of nausea, vomiting, or diarrhea. Intensity should be recorded as:

    0: none
    1: mild
    2: moderate
    3: severe

    Any treatment for these will be recorded as concomitant medications.

  - At the onset of any abdominal pain, the following will be recorded:

    Intensity, recorded as: none, mild, moderate, or severe.

    Duration, documenting any treatment as a concomitant medication.

  - Blood pressure and heart rate at hourly intervals unless more frequent readings are indicated.

  - Time of expulsion, if occurring during the observation period.

  - Any unexpected symptom or clinical finding.

The use of intramuscular sulprostone in combination with mifepristone in previous studies has occasionally precipitated an episode of hypotension usually associated with bradycardia. In extremely rare circumstances this previously utilized treatment regimen has been associated with myocardial infarction and ventricular tachycardia. These complications are very unlikely with the combination of misoprostol and mifepristone. However, any significant fall in blood pressure or significant change in heart rate, however transient, following the administration of misoprostol will be recorded and the subject observed for at least three hours after their blood pressure and heart rate have returned to baseline. In case of chest pain, hypotension or cardiac arrhythmia, an ECG should be performed immediately and if required adequate resuscitation should be undertaken.

The cycle immediately following the administration of mifepristone is ovulatory. Therefore, subjects will be counseled to initiate contraception. Barrier contraception may be initiated within three days of misoprostol administration.

- A gynecological examination will be performed to determine if products of conception remain in the vagina or cervix.

- A very active attempt should be made to contact any subject who fails to appear for the Visit 2 appointment. The administration of misoprostol after Day 3 is strongly discouraged. Misoprostol may be administered between 36 and 60 hours after mifepristone administration.

- If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.

6.3 ~~VISIT~~ 3 (Exit Interview, Day 15 of Study)

Visit 3 will be conducted on Day fifteen (15) of the study. At Visit 3 the following will be performed:

- Clinical and gynecological examination.

- Assessment of severity and duration of uterine bleeding. Subjects who experience bleeding post Day 15 should be followed-up via telephone until the bleeding has stopped or intervention is clinically indicated.

- Assessment of hemoglobin or hematocrit if indicated.

- Verification of any concomitant medications or other therapeutic measures since Visit 2.

- Assessment of expulsion (history, pelvic examination), as well as date and time of occurrence if appropriate.

- Final evaluation of the treatment outcome through the clinical and gynecological examination. If necessary, perform ultrasonography and/or urine pregnancy test.

- In instances where the medical abortion method has failed, either completely or partially, perform the necessary additional surgical procedure. In the subjects for whom a surgical procedure is required, schedule a follow-up visit as per Section 6.6 below.

- Examine the subject's view of her abortion experience including her view of the experience relative to expectations; assessment of discomforts and side effects; timing and place of abortion; satisfaction with the experience; comparison to any previous abortion experience; best and worst features of the method being assessed in the trial; attitude toward self-administration of prostaglandin at home and preference for home or clinic treatment. All responses will be recorded in the case report forms.

- Assure that the subject's case record forms have been completely, accurately and properly filled in.

- A very active attempt should be made to contact any subject who fails to appear for the Visit 3 appointment.

- If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.

6.4 UNSCHEDULED VISITS

At Visits 1 and 2, subjects will be advised that they may return to the study center at any time if they experience medical problems associated with the medical abortion or for any other medical problem. At any unscheduled visits the following will be recorded:

- Reason for the visit.

- Use of any concomitant medications since the last visit.

- Information regarding utilization of any other medical resources.

- Pregnancy status at onset of visit.

- Temperature, blood pressure, heart rate, and hemoglobin.

- Any medication administered during visit as well as any medications prescribed.

- Any procedures conducted during the visit.

- Results of any pathology testing.

Subjects who have a surgical abortion at any unscheduled visit will have the exit interview (As defined in Section 6.3 above) prior to departure from the study center on the day of the surgical abortion, and will not return for the scheduled Visit 3. However, subjects undergoing surgical abortion will be scheduled for a follow-up visit as outlined in Section 6.6 below.

6.5 MEDICAL ADVISORY COMMITTEE

If serious adverse events occur beyond expectation, the decision of whether or not the study should be discontinued or modified will be taken by the Sponsor in consultation with the Medical Advisory Committee.

6.6 FOLLOW-UP

Subjects who are enrolled and receive either or both drugs in the study and undergo surgical abortion at any time during their enrollment will be scheduled for a follow-up visit. This follow-up visit will be scheduled for two weeks post the date of the surgical abortion. At this visit the following will be recorded:

- Brief medical history and clinical examination.

6.7 EARLY WITHDRAWAL FROM THE TRIAL

Subjects may withdraw from the study at any time at their own request. In all cases, the reasons for the subjects withdrawal must be recorded in detail in the case report forms and in the patients medical records. In all cases of withdrawal the subjects must be encouraged to have surgical abortions. If any subject refuses surgical abortion, the investigator must record that the subject understands the risks involved in allowing the pregnancy to continue once drug treatment has begun. **A center must retain its records with respect to a subject who withdraws from the study after ingesting mifepristone and for whom a complete abortion has not been confirmed for a period of at least 30 years following the subject's last visit to the center.**

All efforts will be made to contact subjects who fail to return for the necessary visits (telephone, registered mail). The subject will not be given misoprostol if contacted after 60 hours of the study. A subject may not complete the treatment regimen if severe side effects or symptoms develop after mifepristone administration that, in the opinion of the principal investigator, constitute a threat to the woman's health. Any subjects who do not complete the treatment regimen for any reason will be assessed for the completeness of the abortion, if possible. Any subject who has received mifepristone and has at the time of early termination had an incomplete abortion, as described above, will undergo surgical abortion as described in Section 6.3 above, and will be considered a failure.

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7. ADVERSE EXPERIENCES

7.1 General Aspects

Adverse Reactions

Subjects will be notified of possible adverse reactions; they will be instructed to immediately report all adverse reactions to the investigator.

Any adverse reaction, noticed by the investigator or reported by the subject, including clinically significant lab abnormalities, will be recorded in the appropriate section of the case report form, regardless of its severity and relationship to study drug.

Serious or unexpected adverse events will be immediately reported by the investigator by telephone to:

[redacted]

Vice President, [redacted]

[redacted]

24 hour answering service outside normal business hours

[redacted] will notify the sponsor, and ensure FDA notification. All serious ("any experience that is fatal or life-threatening, is permanently disabling, incapacitating, requires inpatient hospitalization, or causes a congenital anomaly, cancer or is due to overdose") and/or unexpected ("any adverse experience that is not identified in nature, severity or frequency in the current investigator's brochure for the study") adverse reactions must be immediately (within 24 hours) reported by telephone to the Sponsor and a written report must be submitted to the medical monitor within 24 hours.

The initial telephone contact will be followed within 3 days by a detailed report of the event which will include copies of hospital case reports, autopsy reports and other documents, when applicable. The adverse event must be followed through resolution.

The same applies to all subjects who died during the course of the study or within 30 days of completion of treatment irrespective of whether the adverse reaction was judged as related to treatment. In case of a death, copy of the autopsy report should be sent to the sponsor, if performed.

For each adverse reaction, the following information will be entered in the case report form: description of event, onset date, resolution date, severity (1=mild, awareness of sign or symptom, but easily tolerated; 2=moderate, discomfort enough to cause interference with usual activity; 3=severe, incapacitating with inability to do usual activity), drug cause-effect relationship and the outcome of the event. The investigator will also note if any action was taken regarding the test drug (temporarily or permanently discontinued) and if therapy or hospitalization was required.

ETHICAL ASPECTS

A. Informed Consent Form

The purpose of the study, those adverse reactions that are known to occur with the study drugs and the subject's right to withdraw from the study at any time without prejudice, must be explained to each subject in a language she understands. The subject is then required to sign in the presence of a witness an approved informed consent form in a language she understands containing all the above-mentioned information and a statement that the subject will permit examination of his/her study case report forms by a third party. Willing subjects may be interviewed by a representative of the sponsor about her understanding of the risks, benefits, procedures, and the experimental nature of the study.

B. Institutional Review Board

This study will not be initiated until the protocol and informed consent form have been reviewed and approved by a duly constituted Institutional Review Board (IRB) as required by U.S. FDA regulations. It is the responsibility of the investigator to submit the study protocol with its attachments to the IRB for review and approval.

The names and professional affiliations of all the members of the board or the IRB general assurance number must be given to the Sponsor of the study prior to study initiation, along with a signed and dated statement that the protocol and informed consent form have been reviewed and approved by the IRB.

The investigator is committed, in compliance with FDA regulations, to inform the IRB of any emergent problems, serious adverse reactions or protocol amendments.

C. Protocol Amendments

Any amendment to the protocol will be with mutual agreement between the investigator and the Sponsor. All amendments to the protocol will be submitted to the FDA and to the Institutional Review Board (IRB) concerned for review and, if necessary, approval prior to implementation of the changes.

D. Study Monitoring

A pre-study visit will be made by the monitor to the investigative site in order to review the protocol and to ascertain that the facility is adequate for satisfactory conduct of the study, as well as to discuss the obligations of both the sponsor and the investigator.

The investigator will permit a representative of the sponsor or his designate and the FDA, if requested, to inspect all case report forms and corresponding portion of the study subjects original office and/or hospital medical records, at regular intervals throughout the study. These inspections are for the purpose of assessing the progress of the study, verifying adherence to the protocol, determining the completeness and exactness of the data being entered on the case report forms and assessing the status of study drug storage and accountability. During site visits, case report forms will be examined by the study monitor(s) and verified by comparison with corresponding source data (such as hospital and/or office records).

ADMINISTRATIVE ASPECTS

A. Curricula Vitae

The investigator will provide the Sponsor with copies of the curricula vitae of himself/herself and the co-investigators listed on the FDA Form 1572.

B. Data Collection in the Case Report Form

A Case Report Form in triplicate will be provided by the sponsor for each subject to be filled in at each visit. Additional forms will be used for screening of the subjects prior to enrollment. In the event of additional visits, extra case report forms for the unscheduled visits will be filled out. At the visits on Days 1 and 15, acceptability questions will be asked, and the data recorded.

Acceptability questions will be asked on the day of surgical abortion for those having a surgical abortion.

One copy of the forms will be retained by the clinical study site, the other copies will be retrieved by the study monitor at the monitoring visits. All forms will be filled in legibly in black ball point pen. All entries, corrections and alterations are to be initialed and dated by the investigator, co-investigator, or study coordinator making the correction. Corrections will be made by crossing through the incorrect data with a single line so that the incorrect information remains visible, and putting the correct information next to the incorrect data. A reasonable explanation must be given by the investigator for all missing data.

C. Data Retrieval

At intervals during the study and at the conclusion of the study, the study monitor will retrieve signed and dated case report forms from the study site for data entry and analysis. The original and one copy of each page will be retrieved by the monitor. The investigator will keep a copy of all original case report forms and source documents.

D. Records Retention

Except as otherwise explicitly set forth herein, pursuant to applicable federal regulations, the investigator must retain copies of all study records for a period of two (2) years following the date a marketing application is approved for the indication for which the drug is being investigated. If no application is filed or if the application is not approved, the study records must be retained until 2 years after the investigation is discontinued and FDA is notified.

E. Study Termination

Either the investigator or the sponsor may terminate the study at any time for well documented reasons, provided a written notice is submitted at a reasonable time in advance of intended termination.

8. STATISTICAL ANALYSIS

8.1 Population Analyzed

All subjects to whom mifepristone has been administered will be included in the analyses.

A) Efficacy

Efficacy will be determined by each subject's abortion status and history at Visit 3 (Day 15), two weeks post the administration of mifepristone. The pregnancy/abortion status requires a clinical evaluation, including where necessary ultrasonographic and/or urine pregnancy results.

One measure of success will be defined as a pregnancy termination by Visit 3 (Day 15) without the need for surgical or instrumentation procedures except for forceps extraction of ovular tissue fragments extending through the external cervical os. If pregnancy has not been terminated by Visit 3 (Day 15), this will be considered a failure.

FAILURES

Two categories of failures will be recognized. These will be called medical failures and acceptability failures.

Medical failures are of two types:

i) persisting pregnancy at Visit 3 (Day 15).

ii) medically indicated surgical intervention because of:

a) incomplete expulsion at Visit 3 (Day 15).

b) serious adverse advents that warrant early surgical interruption of pregnancy.

Acceptability failures are deemed to have occurred when subjects request surgical interruption of a persisting pregnancy before Visit 3 (Day 15) without medical necessity.

In consequences of this distinction between types of failure, there will be two evaluations of success and failure rates.

The *medical failure rate* (MFR) will be determined by life table analysis on a day to day basis from Visit 1 (Day 1) through Visit 3 (Day 15). Women who request surgical abortions before Visit 3 (acceptability failures) will be considered as censored as of mid-day on the day of the surgical abortion. Persisting pregnancies as of Visit 3 are considered failures. The method success rate is 1-MFR for any day or cumulative analysis. Women with persisting pregnancies of less than two weeks post the administration of mifepristone when last observed (e.g., lost to follow-up) will be treated as censored in mid-day of the last observation in the calculation of gross rates.

The *total failure rate* (TFR) will also be determined by life table techniques using the assumption that some of the subjects with persisting pregnancies are last observed before two weeks post the administration of mifepristone. Daily total failure rates are computed under the assumption that subjects with continuing pregnancies last observed before Visit 3 were last observed in the middle of the day of last observation.

Data will be recorded in the case report forms to allow for the distinction between medical and acceptability failures.

All failures will undergo vacuum aspiration or dilation and curettage. Material will be submitted for pathological examination.

B) Safety

Safety will be assessed utilizing the following parameters:

- Duration and severity of uterine bleeding; data obtained from subject diary, determination of hemoglobin, by treatment (e.g., transfusion, surgical procedure) necessary secondary to heavy and prolonged uterine bleeding.

- Occurrence of any adverse event or abnormal clinical finding (e.g., signs of pelvic infection).

- Adverse events linked to drug administration and abortion (e.g., nausea, vomiting, diarrhea, painful uterine contractions).

- Assessment of heart rate and blood pressure during the observation period following the administration of misoprostol.

Safety data will include all safety parameters at all visits both scheduled and unscheduled, as well as data collected in the subject's diary, of all subjects to whom mifepristone has been administered.

C) Acceptability

Acceptability will be measured by patient interviews at the final discharge visit. The assessments will be made on the basis of answers to questions concerning:

- satisfaction with the information and counseling,
- satisfaction with the procedure,
- comparison to previous abortion experience, where applicable,
- willingness to choose the method again, and,
- willingness to recommend the method to others.

All these variables will be assessed in light of the level of complications, discomforts, and side effects recorded for each patient on both the questionnaire and symptomatology diary.

Acceptability of the regimen will also be determined through a questionnaire for providers.

D) Feasibility of Use in the U.S. Health Care System

Variability is built into the study with regard to: Type of abortion site (hospital clinic, Planned Parenthood clinic, feminist health clinic, private practice, free-standing abortion clinic), ethnicity of patient, socioeconomic status (Medicare, self-pay, insurance, help fund, etc.), and location in inner city, small city, suburb, or rural area. The association of these factors with:

- adherence to the protocol
- complications and side effects
- failure (and type of failure)
- patient satisfaction with medical abortion
- provider comfort with medical abortion

will be analyzed.

8.2.0. A detailed plan, outlining in advance the statistical evaluation of each baseline, safety and efficacy variable, will be submitted to file prior to statistical examination of the data. Essential features of this plan, as presently anticipated, are described below.

8.2.1. Descriptive Statistics: Characteristics of subjects measured at admission through the administration of mifepristone will be summarized. All variables pertaining to safety, efficacy and acceptability will be summarized.

8.2.2. Lifetable Analysis of Efficacy: Single and multiple decrement failure rates for each type of failure and for the total failure rate will be analyzed for each amenorrhea duration, and all durations. Failure rates, by duration of amenorrhea, for age, ethnic group, payment status, and service delivery groups will be determined.

8.2.3. Efficacy Analysis: Multinomial logistic models will be employed to evaluate efficacy. Successful abortion, incomplete expulsion, early surgical interruption due to medical necessity and early surgical interruption at the patient's request (no medical necessity) will serve as the outcome categories used to form response vectors for the models. In one model, the response vector will be comprised of the cumulative log odds over the three types of failure (i.e., incomplete expulsion, medical interruption and requested interruption). In another model, the response vector will be the log odds of these individual types of failure *per se*. In all models, the independent vector will be amenorrhea duration ($\leq$ 49 days, 50-56 days and 57-63 days).

The models will be used to test the overall (omnibus) effect of amenorrhea status. Additionally, pairwise contrasts among the amenorrhea groups will be evaluated. Both the overall effect and pairwise effects will be examined using traditional hypothesis tests to assess the *complete response vector* (i.e. all failure categories considered simultaneously). However, *individual response categories* will be examined in two ways. First, a traditional hypothesis test will be used to conduct a test of the overall affect of amenorrhea. Second, the examination of pairwise amenorrhea group contrasts will take the form of an equivalency test.

All traditional tests will be evaluated using a type I error rate of 0.05. Equivalence tests will be performed using 90% confidence intervals (which mathematically correspond to a type I error rate of 0.05) and an equivalence interval of $\pm$ 5 percentage points.

Single and or multiple decrement life table techniques, as appropriate, will be used to display failure rate probabilities by time, for individual amenorrhea group and all groups combined.The various effects examined using the multinomial logistic models will also be exhibited in tables and/or figures.

8.2.4. Analysis of factors associated with early abortion (Days 1-3) or late abortion (Days 4-15) or Failure will be undertaken by a variety of multivariate techniques. This analysis pertains to aspects of efficacy, safety and acceptability.

8.2.5. Baseline/Safety Analysis. Qualitative baseline and safety variables will be systematically summarized in appropriate patient groupings for examination by the medical reviewer. Descriptive statistics for baseline and safety variables that are suitable for quantitative analysis will be displayed in tables and figures. Furthermore, these variable will be evaluated across amenorrhea groups using linear models, applied to continuous or categorical variables. Continuous variables expected to markedly deviate from normality will be rank transformed to obtain nonparametric tests of significance. Any baseline variable found to exhibit a meaningful difference across amenorrhea groups, will be considered for use as covariate or blocking factor in the efficacy analysis. As a conservative measure to increase statistical power, variables exhibiting p-values of 0.20 or less will be singled out to assess their potential relevance to the safety and efficacy of the study drug.

Analysis of variables associated with need for transfusion and with severe cardiovascular adverse events will be undertaken.

8.2.6. Acceptability Analysis: Analysis of variables associated with acceptability within each duration of amenorrhea and overall shall be undertaken using both univariate and multivariate techniques.

9. RISK-BENEFIT ASSESSMENT

Experience gained to date with the use of mifepristone and prostaglandin for the termination of early pregnancy indicates that this has few side effects and a frequency of short-term complications that is comparable to that observed after vacuum aspiration. The most common complaints during treatment, particularly following administration of the prostaglandin, are lower abdominal pain, nausea, vomiting and diarrhea. In addition, bleeding for several days is common. For these complaints, appropriate medication can be prescribed when required. Occasionally, heavy uterine bleeding may necessitate emergency curettage and, very rarely, blood transfusion.

The approximate failure rate, according to the experience gained from women who have had this treatment in Europe, up to 49 days is 5%. Therefore approximately 5% of the subjects in this trial treated up to 49 days of amenorrhea will be expected to undergo surgical termination of pregnancy. It is possible the failure rate will be higher in the older pregnancies.

Following a treatment regimen involving the intramuscular injection of the prostaglandin analog sulprostone, in a very low percentage of cases (one in 20,000), serious cardiovascular complications have been observed, including one case of fatal myocardial infarction. These complications have been most often associated with subjects who were heavy smokers, and still these complications are extremely rare. There is no evidence that misoprostol, a different class of prostaglandin, which is widely prescribed for longterm use in the prevention and treatment of peptic ulcer disease, is associated with any such cardiovascular side effects.

All subjects will be informed as to the potential complications. Centers participating in the trial will ensure that qualified personnel and necessary equipment and supplies are available at all time to deal with any complications.

Studies conducted in mice and rats have shown that mifepristone does not have any teratogenic effects. There are insufficient data to evaluate the effects of mifepristone on the human fetus. In one subject in France who took mifepristone and failed to abort, pregnancy was terminated at 18 weeks because of fetal abnormalities. The precise relationship to mifepristone could not be established[6]. Thus, in the event of a continuing pregnancy, surgical abortion should be performed. Misoprostol has been reported to be teratogenic and is reported to be associated with malformations of the scalp, cranium and other abnormalities[7].

The benefits of this form of medical termination of pregnancy are that most women participating in the study can be expected to have a complete abortion and will not be exposed to the risks associated with surgical abortion, particularly the risks of physical trauma (e.g., cervical laceration, uterine perforation, etc). Nor does medical abortion carry any anesthetic-related risk.

No financial renumeration will be offered to potential study participants.

10. SIGNATURES

I have read the forgoing protocol and agree to conduct the study as outlined.

Signature of Investigator — 10/17/95 (M D Y)

Signature of Sponsor — / / (M D Y)

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Table 1

	Visit 1	Visit 2	Visit 3
Counseling	X		
Medical, OB-GYN History	X		
Medical Examination	X	X	X
Pelvic Examination	X	X	X
Urine Pregnancy Test	X		X*
Quant. Serum ßhCG	X		X*
Vaginal Ultrasound	X	X*	X*
Blood Typing including Rh	X		
Hemoglobin or Hematocrit Determination	X		X*
Administration of Mifepristone	X		
Administration of anti-D globulin		X*	
Administration of Misoprostol		X	
Interview and Review of Diary		X	X

* - To be conducted if indicated

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APPENDIX 1

PROTOTYPE INFORMED CONSENT

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 A

1. Purpose and aims of the study

It is possible to induce abortion in women with unwanted pregnancies by taking mifepristone in combination with a prostaglandin (misoprostol). Mifepristone is a drug which blocks the action of progesterone, a hormone needed to maintain pregnancy. One of mifepristone's actions is to interrupt pregnancy in its early stages. Prostaglandins are natural substances made by the lining of the womb during menstruation and cause contraction of the womb. During the early stages of pregnancy, mifepristone plus misoprostol cause abortion in approximately 95 per cent of women. Major advantages of this method of pregnancy termination are that no surgical instruments are pushed into the womb. Over 150,000 women in 20 countries have used mifepristone and a prostaglandin as a medical method of pregnancy interruption. Mifepristone and misoprostol have been used by over 50,000 women at the dose to be used in this study. The dosage to be studied has been approved for routine use in France for women who have been pregnant for seven weeks or less. Mifepristone in combination with a prostaglandin has also been approved for use in China, Britain and Sweden. In the latter two countries, it is used in women who are pregnant for nine weeks or less.

The aims of the present study are to determine the safety, efficacy and acceptability of mifepristone plus misoprostol for pregnancy termination in women who are 63 days or less from the first day of the last menstrual period. Three groups of women who are less than 50 days; 50 through 56 days and 57 through 63 days from the first day of the last menstrual period will be included in the study. This study is being performed as a requirement for registration of mifepristone plus misoprostol with the U.S. Food and Drug Administration (FDA) so that these products can be used for pregnancy termination in the U.S.

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 A

2. Clinic visits

I understand that at my initial visit (visit 1) I will receive counseling about the method, and a urine and blood sample will be collected to make sure I am pregnant. I will be given a physical, and a pelvic exam and my medical history will be taken. Using a vaginal ultrasound, which is a small probe that is placed in the vagina, the duration of my pregnancy will be determined. Also I will be given a blood test for the Rh factor in my blood. If I have an Rh negative blood type, I will be given an injection at the second visit to prevent the development of antibodies that could endanger any future pregnancy. In order to terminate my pregnancy, I will take three tablets of mifepristone (first medication) orally in the presence of study personnel. Two days later, I will return to the clinic (visit 2) even if I believe I have aborted and will take two misoprostol tablets (second medication) by mouth if I have not aborted. If I take the second medication, the duration of my stay at the clinic at the second visit will be approximately four hours, during which time I will be closely monitored by the study team. During this time, there is an 60-80% chance that abortion will occur. If I come to the clinic in a car, I will be sure to arrange for someone else to drive me home from this visit, and understand that I will not drive myself home. I understand that if the abortion does not occur at the clinic, it is likely to occur at home and I may continue to have uterine bleeding similar to a heavy menstrual period for several days. I should use sanitary napkins until the uterine bleeding or spotting ends and not use tampons. As with surgical abortion, I cannot resume douching until the bleeding stops (about 10-12 days). I should not resume sexual intercourse for eight to ten days after taking the prostaglandin, by which time most abortions would have been completed.

I understand that I may see the product of conception on my sanitary napkin or in the toilet. This may happen at the clinic, at home or work. Through the seventh week after conception, this product is called an embryo; it is smaller than a quarter and is usually embedded in a blood clot. Even if I see the products of conception, I will not be able to tell whether the method has been effective as part of the placenta may still remain in the uterus. This is why it is important to return to the clinic for a follow-up, visit 3, so that the clinic staff can determine if the abortion is complete.

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 A

A further appointment will be made for me to return to the clinic two weeks after taking the first tablet (visit 3), to ensure that the treatment has been effective. If the treatment has not been effective, then a surgical procedure called vacuum aspiration or dilatation and curettage will be carried out at that time to complete the abortion. This is the same surgical procedure that would have been used had I elected to undergo surgical abortion in the first instance. I will be sure to have arranged for someone else to drive me home from this visit, and understand that I will not drive myself home. If I notice a vaginal discharge with odor after treatment, this may indicate an infection. I will contact my physician for an appointment.

I understand that bleeding may continue beyond my third visit. If this occurs the clinic will contact me by telephone to determine if it has stopped or if I need additional treatment.

I understand that there are no indications at present that use of an antiprogestin to end a pregnancy has prevented or harmed a woman's ability to have a baby in the future. Women who have taken mifepristone have been able to conceive and subsequently bear a healthy child. Since it is possible to become pregnant again after the abortion, I will be asked to select and use a contraceptive method.

3. Benefits

I understand that an advantage of the mifepristone/misoprostol medical method for pregnancy termination is that it avoids a surgical procedure. There is no anesthesia-related risks or risk of uterine perforation or cervical canal injury which may rarely be observed after surgical termination of pregnancy. Another benefit is the satisfaction of participating in the study that will make mifepristone/misoprostol available to women in the U.S.

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Exhibit \\ Page 33 of 38

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 A

4. Risks and discomforts

I understand that drawing blood for the tests at the first visit may be associated with discomfort, bruising, and possibly infection at the site of withdrawal. I understand that experience gained so far with the combination of drugs and the termination of early pregnancy indicates that this therapy has few side effects. The frequency of short-term complications are comparable to that observed after surgical abortion performed by vacuum aspiration. The most common complaint during treatment (particularly following administration of the second medication) is lower abdominal pain or cramps which are similar to those associated with a very heavy menstrual period. I will receive appropriate medication for pain when required. I understand that I should not take aspirin, Motrin®, ibuprofen (Advil®) or any other drug known to block the action of prostaglandins. However, I may take Tylenol® and I may receive stronger medications for pain from my doctor. I understand that cramps and abdominal pains are usual and an expected part of the abortive process. Nausea, vomiting, and diarrhea have been observed following administration of the second medication. Therefore, at the second visit it is necessary to remain at the clinic under appropriate medical supervision for approximately four hours before returning home. Uterine bleeding, similar to a heavy period and lasting at least one week, may be expected. In rare instances very heavy uterine bleeding may occur requiring surgical abortion and/or blood transfusion.

I understand that it is not advisable to allow a pregnancy to continue after taking mifepristone and/or misoprostol, since the full effects of mifepristone on the fetus are not known and misoprostol administration in early pregnancy has been associated with abnormal development of the fetus. I understand that abortion after mifepristone/misoprostol is successful in termination of pregnancy in approximately 95% of treated women. When abortion is incomplete, vacuum aspiration or dilatation and curettage are recommended to terminate bleeding and prevent anemia. ***When abortion does not occur, surgical termination of pregnancy is recommended because of the possible risk to the fetus. I have previously agreed to this procedure.***

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 A

There have been no serious heart conditions in the 52,000 women using the combination of drugs in the study for pregnancy termination. However, serious cardiovascular complications, including one fatal heart attack occurred during medical abortion using a different drug combination. These heart conditions have occurred usually in women who are heavy smokers or have increased blood fats, diabetes, high blood pressure, or family history of heart disease. This risk also increased in women who are over 35 years of age. These complications have been seen only following an injected prostaglandin and are rare (one in 20,000 cases). To date there is no evidence that the oral prostaglandin (misoprostol) that I will be taking in this study and which has been used widely for prolonged periods of time in the prevention of stomach ulcers, is associated with such cardiovascular side effects.

5. Alternative Statement

I know that my pregnancy could be terminated by a surgically performed abortion procedure (dilatation and curettage or vacuum aspiration). The possible advantages and disadvantages of a surgical rather than a medical termination have been explained to me. The advantages of surgical termination of pregnancy is that this is a one day procedure. The risks associated with surgical abortion are minimal. These include the risk of an anesthetic procedure. In the U.S., less than 1% of patients who undergo a surgical abortion experience a major complication associated with the procedure such as a serious pelvic infection, cervical tear, bleeding requiring a blood transfusion or unintended major surgery (for a uterine perforation).

6. Physical Injury Statement

If I require medical treatment as a result of physical injury arising from my participation in this study, immediate, essential, short-term medical care and treatment as determined by the doctors in this study will be made available without charge to me. There will be no monetary compensation for any other care, but medical consultation and appropriate referral services are available. Further information on the availability of medical care and treatment for any physical injury resulting from my participation in this study may be obtained from the Investigator, Dr. _____ (telephone:_____).

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Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 11 Page 35 of 38

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 A

7. Whom to Call in an Emergency

I understand that if severe uterine bleeding, or abdominal pain, or any other medical emergency arises in association with this method, I will report immediately to (institute, address, telephone no.) In addition, I will contact Dr. _____

(telephone:_____). If he or she cannot be reached in a medical emergency related to the study, I may contact Dr. _____ (telephone:_____).

8. Offer to Answer Questions and Freedom to Withdraw from the Study

I have been told that I may withdraw from the study at any time without jeopardy to my present or future medical care from the hospital or clinic. If I withdraw I will be offered a surgical abortion. I have been told to contact Dr. _____(telephone:_____ or Dr. _____ (telephone:_____ if I have any questions about the research. These physicians may appoint their associates to answer my questions.

I also understand that the Principal Investigator may require me to withdraw from the study, if in his/her medical judgement it is in the best interest of my health or if it becomes impossible for me to follow the experimental procedure of this study.

I understand that, if my treatment under the study does not result in an abortion, and I refuse surgical abortion and continue with my pregnancy, I risk, and the infant may risk, complications, including fetal or infant malformation.

9. Confidentiality

I understand that information obtained in this study will be transmitted only in a form that cannot be identified with me, and that all records will be kept in a locked cabinet. I understand that the Population Council or their designated monitors, as well as the U.S. Food and Drug Administration may request access to my medical records.

I understand that I may be asked to be interviewed by a representative of the sponsor. The interview will be conducted in the language that I speak and will verify that I understand the risks, benefits, procedures, and the experimental nature of the study. If I do not agree to be interviewed, this will not affect my present or future medical care from the hospital or the clinic, or my participation in the study. I understand that I can change my mind at any time. All information will be kept confidential.

EVALUATION OF THE EFFICACY, SAFETY AND ACCEPTABILITY OF MIFEPRISTONE AND MISOPROSTOL IN INDUCING ABORTION IN PREGNANT WOMEN WITH AMENORRHEA OF UP TO 63 DAYS

PROTOCOL NUMBER: 166 A

10. Subject's Statement

I, the undersigned, have had the risks and benefits of this study explained to me in a language that I understand. I agree to participate in this study as a volunteer subject.

Date	Signature of Volunteer

11. Investigator's Statement

I, the undersigned, have explained to the volunteer in the language which she speaks the procedures to be followed in this study and the risks and benefits involved.

Date	Signature of Investigator
Date	Signature of Witness to the Above Signatures and Explanation

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 11 Page 37 of 38

MEDICATION/ INVENTORY
MIFEPRISTONE/MISOPROSTOL STUDY

Site #: _____ Initial Inventory: _____

Patient Number	Tablets Dispensed Mifepristone and Date		Tablets Dispensed Misoprostol and Date

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 11 Page 38 of 38

_____ _____
SIGNATURE OF INVESTIGATOR DATE

_____ _____
SIGNATURE OF MONITOR DATE

10. SIGNATURES

I have read the forgoing protocol and agree to conduct the study as outlined.

[redacted]

Signature of Investigator

8/16/94
M D Y

Signature of Sponsor

/ /
M D Y

APPEARS THIS WAY
ON ORIGINAL

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 12 Page 1 of 4

10. SIGNATURES

I have read the forgoing protocol and agree to conduct the study as outlined.

Signature of Investigator
Suzanne T. Poppema, MD

4 / 12 / 95
M D Y

Signature of Sponsor

/ /
M D Y

APPEARS THIS WAY
ON ORIGINAL

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 12 Page 2 of 4

10. SIGNATURES

I have read the forgoing protocol and agree to conduct the study as outlined.

Signature of Investigator — 10, 17, 95 (M D Y)

Signature of Sponsor — / / (M D Y)

APPEARS THIS WAY
ON ORIGINAL

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 12 Page 3 of 4

10. SIGNATURES

I have read the forgoing protocol and agree to conduct the study as outlined.

Signature of Investigator — 10/19/95 (M D Y)

Signature of Sponsor — / / (M D Y)

APPEARS THIS WAY
ON ORIGINAL

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 12 Page 4 of 4

MIFEPRISTONE STUDY
MODIFICATIONS TO THE PROTOCOL
FOLLOWING THE OCTOBER 3-4, 1994
INVESTIGATOR'S MEETING

Protocol:

Cover Sheet:	Change: The Population Council **to** The Population Council, Inc.
	Change: Written authorization from The Population Council, **to** written authorization **of** The Population Council
Table of Contents: 6.5:	Change: SAFETY ASSESSMENT COMMITTEE **to** MEDICAL ADVISORY COMMITTEE
P. 3: First paragraph:	The word either was added in reference to parenteral or vaginal prostaglandins in combination with mifepristone
P. 3: Last paragraph:	Change: heart condition **to** heart complications
P. 4: Third paragraph:	Change: as close as possible to **as closely** as possible
P. 4: Last paragraph	Add: Subject shall visit the study center three times **unless state law requires an additional, initial informational visit with a mandatory waiting period before the process can begin.**
	Add: At the initial visit (Day 1) **; after any required statutory waiting period.**
P.5: second paragraph:	Change: institutional insurance **to** general liability insurance
P.6:	**Add: 4.1.3 Residents of the United States**
P. 6:	**Add: 4.2.9 Resident of the United States**
P. 7: 4.3.2	delete **repeated**
P. 7: 4.3.5	Add: **or hematocrit below 30%**
P. 7: 4.3.7	Delete prior uterine surgery where the myometrium has been cut Add: **Subjects with an IUD in place.**

P. 7: 4.3.15 -		Change to:	Women who cannot reach the source of emergency medical care that serves the abortion center within one (1) hour from (a) their home or place of work and (b) the abortion center.
P. 8: Section 5.2:		Clarification that 600 mg of mifepristone will be administered orally.	
P. 9: Section 5.3:	A)	Change to:	Mifepristone will be provided as 200 mg tablets of micronized mifepristone
	B)	Change to:	Misoprostol will be obtained locally by each investigator as 200 µg tablets of commercially available misoprostol.
P. 9: Section 5.4:	A)	Change to:	Mifepristone will have a label which will include product identification, expiration date, and drug dose. In addition the following will be printed on the labels: CAUTION: New drug. Limited by Federal Law to Investigational Use. All medication packets will be labelled with the protocol number.
	B)	Change to:	Misoprostol will be obtained locally by each nvestigator as 200 µg tablets of commercially available misoprostol and dispensed from the center pharmacy.
P. 9: Section 5.5: paragraph 1		Change:	hypertension to hypotension
		Change:	should be avoided to **must** be avoided
P. 10: Section 6.1:		Change:	Serum ßhCG test to quantitative serum ßhCG.
		Change:	Determination of blood group and Rh status to Determination of Rh status and where routinely collected, the blood group.
P. 10: - Last paragraph:		Add:	**No more than** 240 ml.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 13 Page 2 of 5

P. 11: - Second paragraph:	Change:	Subjects will be given written information to Subjects will be given a copy of the informed consent and patient diary card.
	Change:	..... which receives patients ..... to which **cares** for patients
Section 6.2:	Add:	**If the patient believes that expulsion occurred prior to Visit 2, the date and time will be recorded on the case report form as they were noted in the subjects diary. Since it is difficult to confirm that an abortion at this time is complete, nearly all subjects will require misoprostol. If however, the physician can verify unequivocally that complete abortion has occurred, the misoprostol will not be administered. If the abortion is incomplete or if there is any uncertainty about the completeness of the abortion, the misoprostol will be administered.**
Last paragraph:	Delete: Add:	(Rhogam) **, if indicated.**
P. 12: First paragraph :	Add:	**No more than** 240 ml
Second paragraph: Last sentence	Delete:	if necessary
P. 13: Section 6.2: Second to Last paragraph	9/6/94 last paragraph Changed to:	A very active attempt should be made to contact any subject who fails to appear for the Visit 2 appointment. The administration of misoprostol after Day 3 is strongly discouraged. Misoprostol may be administered between 36 and 60 hours after mifepristone administration.
P. 13: Section 6.2: Last paragraph	Add:	**If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.**

P. 13: Section 6.3:	Add:	**Subjects who experience bleeding post Day 15 should be followed-up via telephone until the bleeding has stopped or intervention is clinically indicated.**
P. 14: after last paragraph	Add:	**If the center is aware of any subject who misses Visit 2 and does not appear for Visit 3, or who otherwise determines to carry her pregnancy to term, the center shall retain its records relating to such subject through the date on which she was last seen at the center for a period of thirty (30) years following such date.**
P. 15: Section 6.5:	Change Heading:	Safety Assessment Committee to Medical Advisory Committee.
	Change Body:	Safety Assessment Committee to Medical Advisory Committee
P. 16: Section 6.7: first paragraph	Add:	**A center must retain its records with respect to a subject who withdraws from the study after ingesting mifepristone and for whom a complete abortion has not been confirmed for a period of at least 30 years following the subject's last visit to the center.**
P. 16: Section 6.7: Second paragraph	Change:	Day 6 to 60 hours
P. 18: Section A:	Change:	study drug to study drugs.
P. 20: Section D:	Add:	**Except as otherwise explicitly set forth herein,**
P. 21: Seventh paragraph:	Change:	submitted for histological examination to submitted for pathological examination
P. 27:	Add:	**Hemoglobin or Hematocrit Determination, Quant. Serum ßhCG**
	Change:	Administration of Rhogam to Administration of anti-D globulin

Informed Consent:

Section 1 Change: Approximately 250,000 to over 150,000

Section 2 Clinic Visits:
Second paragraph last sentence:

Change: or third visit **to,** visit 3,

Section 2 Clinic Visits: Add: paragraph 4

I understand that bleeding may continue beyond my third visit. If this occurs the clinic will contact me by telephone to determine if it has stopped or if I need additional treatment.

Section 8: After last paragraph
Add: **I understand that, if my treatment under the study does not result in an abortion, and I refuse surgical abortion and continue my pregnancy, I risk, and the infant may risk, complications including fetal or infant malformation.**

APPEARS THIS WAY
ON ORIGINAL

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 13 Page 5 of 5

INSTITUTIONAL REVIEW BOARD

Under the Auspices of

[ ]

May 25, 1995

Suzanne Poppema M.D.
Aurora Medical Services, Inc. P.S.
1207 North 200th Street, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

On May 24, 1995 this IRB met regarding the Population Council clinical trial entitled: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days", protocol #166A/B. This IRB meeting all Federal Regulations for membership requirements and consisting of 8 individuals (of which 6 were in attendance), of different backgrounds and professions met and approved (by majority) the revised protocol dated May 5, 1995 which includes Amendment #1, Amendment #2, Amendment #3, and the revised informed consent.

The IRB members included the following professions:

Physicians, Clergy, School Principal, Nurse, a Community Activist and a Lawyer

Enclosed please find a copy of the protocol with Amendments #1, #2, and #3, along with the informed consent form. Both bear the stamped approval of this IRB. If needed, please have any informed consent forms translated and submitted to this IRB for a formal approval, as soon as possible.

Please note that all regulatory requirements previously stipulated remain in effect.

Your continuing cooperation with this IRB is greatly appreciated.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 14 Page 1 of 10

INSTITUTIONAL REVIEW BOARD

March 10, 1995

Suzanne Poppema, M.D.
Aurora Medical Services, Inc. PS
1207 North 200th Street, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

You will recall that Federal Regulations require that investigators conducting clinical studies provide the responsible Institutional Review Board (IRB) with periodic reports on the progress of their studies.

It is the policy of this IRB to require such reports at intervals of not more than six (6) months from the date that approval is granted. Also required is a final study report at the completion or premature termination of the study. Should the study be completed in less than six (6) months, then a final study report is all that is required.

According to our records, it is nearly six (6) months since the last update on your study:

> Population Council study: "Evaulation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days" (protocol #166 A/B)

This letter is a reminder that a six (6) month progress report or a study completion report is now due.

If you have not yet completed your study, kindly provide this IRB with the required progress report without delay so as to ensure continued approval of your study.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 14 Page 2 of 10

On the other hand, if you have already completed your study, please submit a final study report.

In order to facilitate the reporting procedure for you, a Study Progress/Final Report Form is enclosed. Please complete and sign the form and return it to the undersigned at the above address.

Sincerely

INSTITUTIONAL REVIEW BOARD

January 24, 1995

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

Please be advised that the Institutional Review Board under the auspices of
s in receipt of the Adverse Event Reports for the study entitled, "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days (Protocol #166 A/B)".

The IRB has received the following patients' Medwatch Forms:

Investigator	Patient #
	12
	15
	22
	33
	50
	76
	61

Patient I.D.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 14 Page 4 of 10

The Medwatch Forms and any available reports were sent to you by Program Manager. While are not utilizing this IRB, any serious adverse events requiring notification to FDA must be reported to all participating investigators and their IRBs. Please insure that you maintain these reports in compliance with federal regulations.

The IRB is aware of these adverse events and has not determined any increased risk to the patient or a change in the risk to benefit ratio. These side effects have been reported in previous clinical trials of the combination of drugs and ongoing safety evaluation is being maintained.

Sincerely,

INSTITUTIONAL REVIEW BOARD

December 14, 1994

Suzanne Poppema, M.D.
Aurora Medical Services, Inc.
1207 N. 200th, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

Please be advised that the Institutional Review Board under the auspices of [redacted] is in receipt of the five (5) Adverse Event Reports for the study entitled, "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days (Protocol #166 A/B)".

The IRB has the following patients' Medwatch Forms:

Investigator	Patient #
Dr. Vargas	#005
Dr. Haskell	#027
	#033
	#036
	#042

The Medwatch Forms and any available reports were sent to you by [redacted] Program Manager, on November 23, 1994 (for patient #005) and on December 6, 1994 (the four patients from Dr. Haskell's site). Please insure that you maintain these reports in compliance with federal regulations.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 14 Page 6 of 10

The IRB is aware of these adverse events and has not determined any increased risk to the patient or a change in the risk to benefit ratio. These side effects have been reported in previous clinical trials of the combination of drugs and ongoing safety evaluation is being maintained.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 14 Page 7 of 10

INSTITUTIONAL REVIEW BOARD

October 27, 1994

Suzanne Poppema, M.D.
Aurora Medical Services, Inc. PS
1207 North 200th Street, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

On Thursday, October 27, 1994, under the provisions of Expedited Approval, I reviewed and approved the changes to the Population Council protocol entitled: "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days", protocol #166A. The changes from the previously approved protocol were of an administrative nature that do not pose any additional risk to the patient or increase the risk to benefit ratio.

Also, I am enclosing a copy of the Informed Consent Form approved for use at your site that bears the stamped approval of the Institutional Review Board under the auspices of . Please be sure to utilize this informed consent in obtaining patient enrollment at your site.

Please note that all regulatory requirements previously stipulated remain in effect.

Your continuing cooperation with this IRB is greatly appreciated.

Sincerely,

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 14 Page 8 of 10

/48

INSTITUTIONAL REVIEW BOARD

October 12, 1994

Suzanne Poppema, M.D.
Aurora Medical Services, Inc. PS
1207 North 200th Street, Suite 214
Seattle, WA 98133

Dear Dr. Poppema:

Thank you for your request to this IRB of September 15, 1994 for review and approval to conduct a study under the Population Council protocol entitled, "Evaluation of the Efficacy, Safety and Acceptability of Mifepristone and Misoprostol in Inducing Abortion in Pregnant Women with Amenorrhea of Up to 63 Days", protocol #166A and #166B. The IRB is aware that both protocols are identical and that desgination of investigators to either protocol will be considered an administrative procedure not affecting the conduct of the study.

This will inform you that on October 12, 1994, this IRB, meeting all Federal Regulations for membership requirements and consisting of 7 individuals of different backgrounds and professions met and approved (by majority) your site to conduct the above mentioned study.

The IRB members included the following professions:

Physicians, Clergy, School Principal, Nurse, a Community Activist and a Health Charity Executive

The Protocol (revised and dated October 12, 1994), the attached Informed Consent Form be utilized at your site, your C.V., pre-investigational site visit and other regulatory documents were reviewed and approved by majority voting.

Please be informed that all documentation required for IRB review to conduct your proposed study has been approved. A copy of the approved consent form is attached.

Suzanne T. Poppema, M.D.
Seattle, WA CFN 3032921
EI: 11/01/99-11/05/99
Exhibit 14 Page 9 of 10

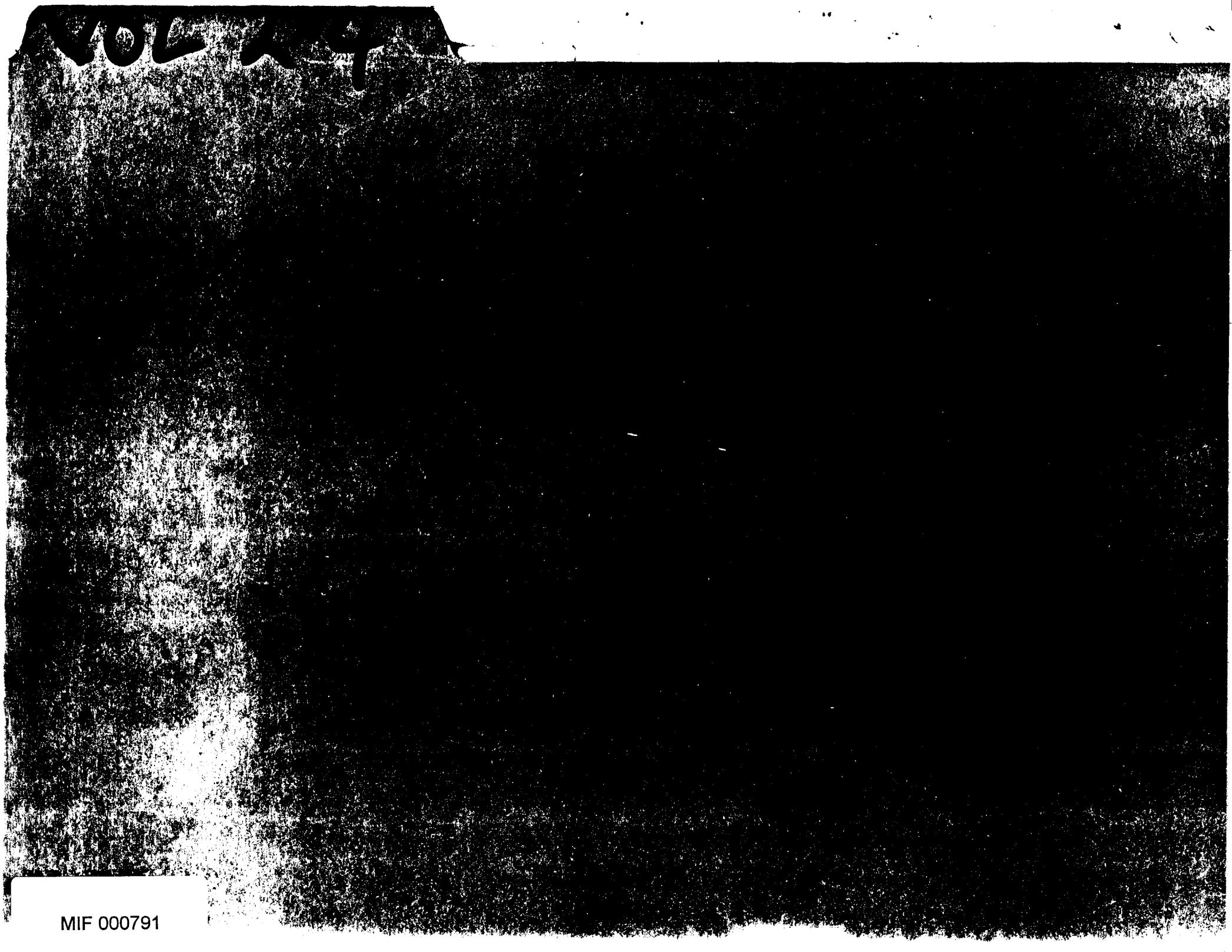
It is also a regulatory requirement that you promptly inform this IRB of any proposed changes in the approved research during the period for which IRB approval has been given. Furthermore, no such proposed changes may be initiated without IRB review except where necessary to eliminate apparent immediate hazards to the study patients or subjects.

Investigators conducting studies under the surveillance of this IRB are required to report all adverse reactions of either an unusual nature, unusual frequency or unusual severity to the Chairman without delay and in no event later than ten (10) working days after the event.

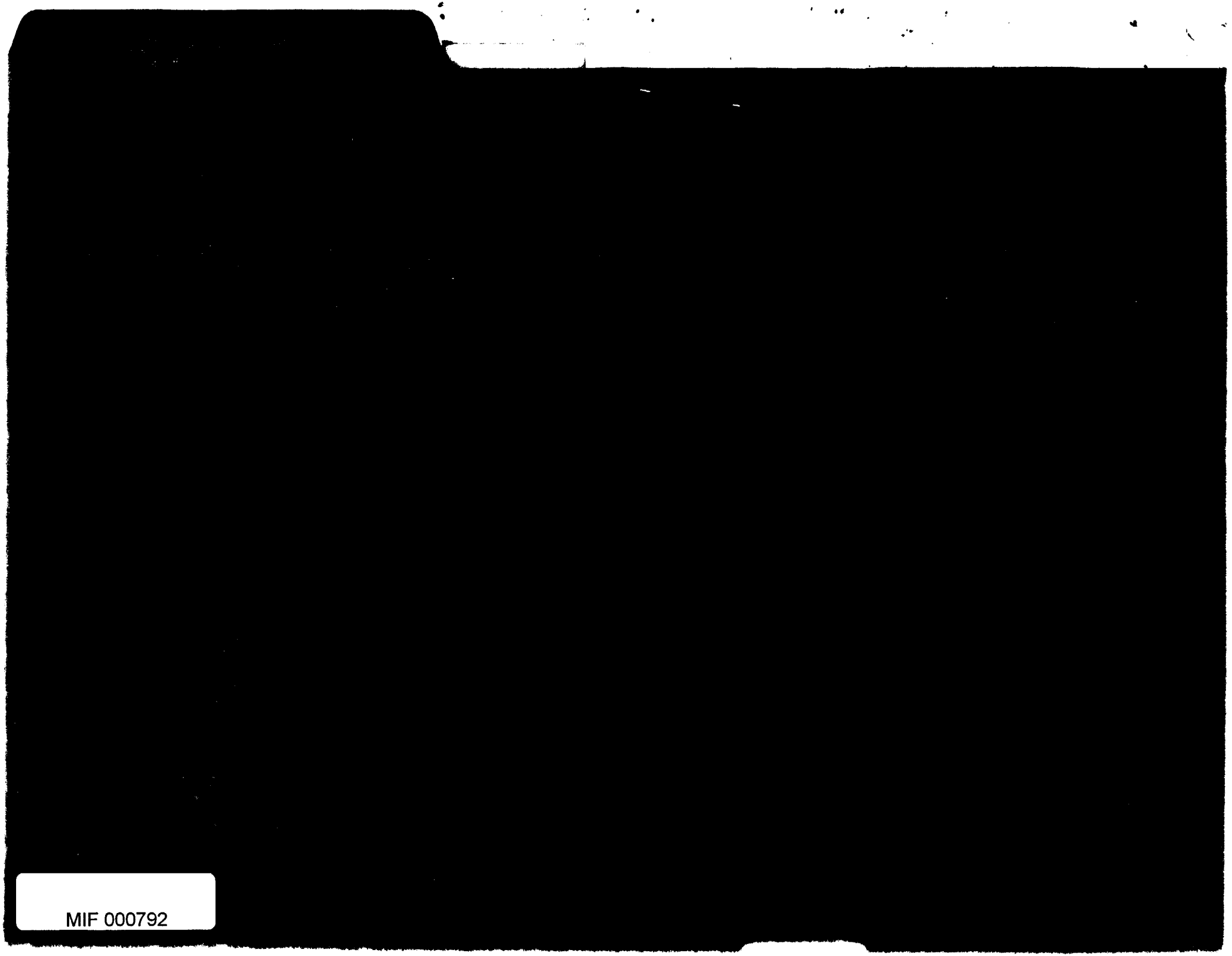
A further regulatory requirement is that the IRB receives periodic reports on the progress of your study. For the purposes of this IRB such reports must be submitted to the chairman of the IRB at the above address at regular intervals of not more than six (6) months. The initial six month follow-up report is due April 12, 1995. This regulation must be adhered to and is the investigator's responsibility. If the reports are not received within a reasonable length of time from the date required, IRB approval may be withdrawn. Also, the IRB is to be informed of the date of completion (or premature termination giving the reasons for termination) of your study and supplied with a final report at that time. Should your study be completed in less than six months, then a final study report is all that is required.

Your cooperation with the IRB with regard to these regulations will be much appreciated.

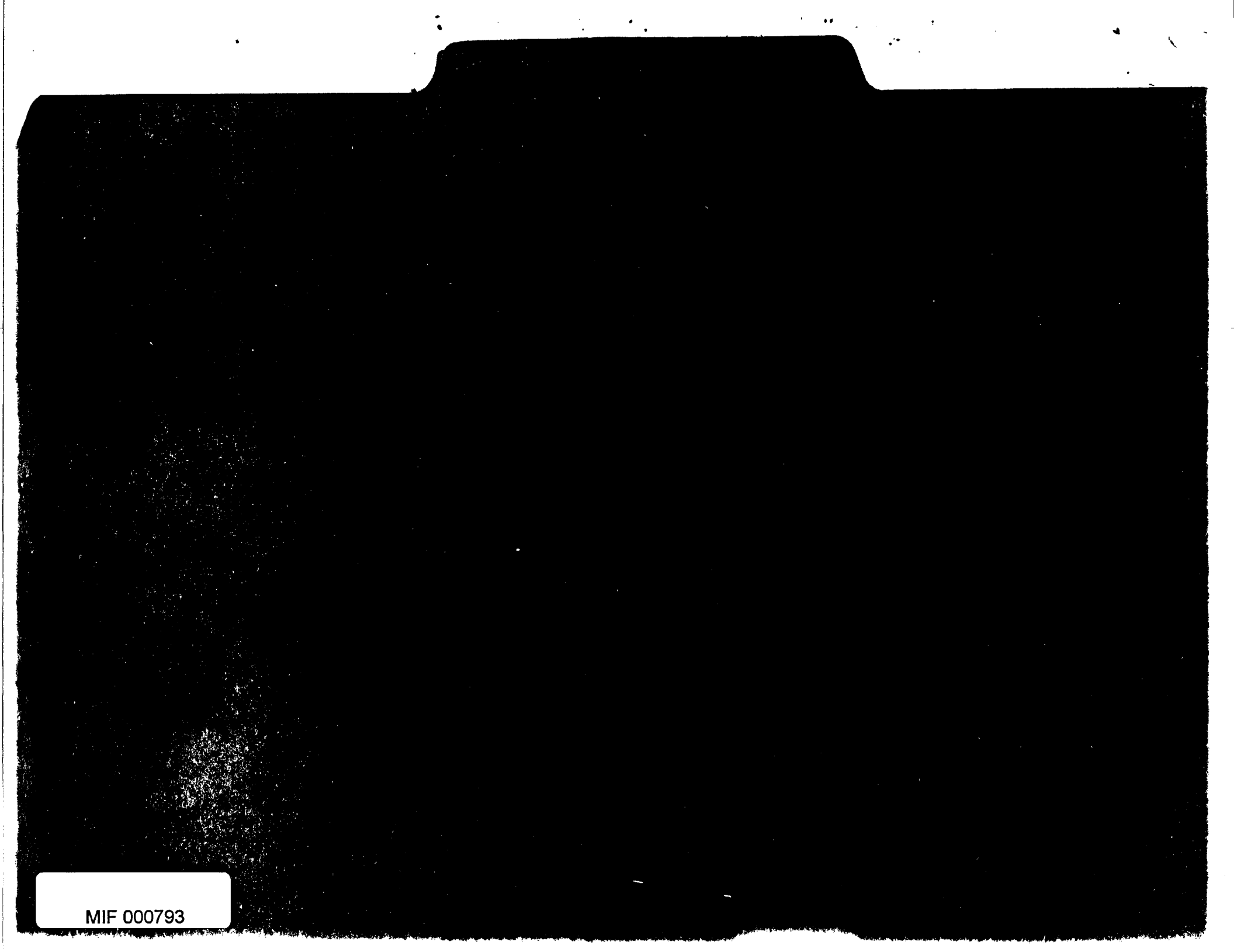
Sincerely,



MIF 000791



MIF 000792



MIF 000793

Appendix D, Table 5a
Adverse Events [1] By Center
(Safety Evaluable Patients)

Center: MISHELL (#1)

Body System/Event [2]	Gestational Age Group [3]	Total Number of Pts	Number of Pts w/Event	Fisher's exact p value	Number of Events	Severity: Mild	Moderate	Severe	Unknown
ANY EVENT	≤63 Days (All)	204	198 (97%)	0.4929	1131	405 (36%)	386 (34%)	340 (30%)	0
	≤49 Days (Group 1)	145	139 (96%)		766	296 (39%)	257 (34%)	213 (28%)	0
	50-56 Days (Group 2)	40	40 (100%)		255	75 (29%)	93 (36%)	87 (34%)	0
	57-63 Days (Group 3)	19	19 (100%)		110	34 (31%)	36 (33%)	40 (36%)	0
SKIN AND APPENDAGES DISORDERS									
ANY EVENT	≤63 Days (All)	204	8 (4%)	0.7173	8	6 (75%)	2 (25%)	0	0
	≤49 Days (Group 1)	145	6 (4%)		6	5 (83%)	1 (17%)	0	0
	50-56 Days (Group 2)	40	1 (3%)		1	1 (100%)	0	0	0
	57-63 Days (Group 3)	19	1 (5%)		1	0	1 (100%)	0	0
ACNE	≤63 Days (All)	204	1 (<1%)	1.0000	1	1 (100%)	0	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	1 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
PRURITUS	≤63 Days (All)	204	1 (<1%)	1.0000	1	1 (100%)	0	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	1 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
PRURITUS GENITAL	≤63 Days (All)	204	2 (<1%)	1.0000	2	2 (100%)	0	0	0
	≤49 Days (Group 1)	145	2 (1%)		2	2 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0

[1] Includes all adverse events reported at any point in the study, regardless of causality.
[2] NOS = Not otherwise specified
[3] Gestational age group was assigned by the investigator based upon menstrual history, pelvic examination and vaginal ultrasonography.
[4] Events in this body system occurred during the study blood sampling.

Appendix A.1, Tables 16 and 25

Appendix D, Table 5a (Continued)
Adverse Events [1] By Center
[Safety Evaluable Patients]

Center: MISHELL (#1)

Body System/Event [2]	Gestational Age Group [3]	Total Number of Pts	Number of Pts w/Event	Fisher's exact p value	Number of Events	Severity: Mild	Moderate	Severe	Unknown
SKIN AND APPENDAGES DISORDERS (cont.)									
SWEATING INCREASED	≤63 Days (All)	204	4 (2%)	0.2125	4	2 (50%)	2 (50%)	0	0
	≤49 Days (Group 1)	145	2 (1%)		2	1 (50%)	1 (50%)	0	0
	50-56 Days (Group 2)	40	1 (3%)		1	1 (100%)	0	0	0
	57-63 Days (Group 3)	19	1 (5%)		1	0	1 (100%)	0	0
MUSCULO-SKELETAL SYSTEM DISORDERS									
ANY EVENT	≤63 Days (All)	204	4 (2%)	0.7159	4	2 (50%)	2 (50%)	0	0
	≤49 Days (Group 1)	145	4 (3%)		4	2 (50%)	2 (50%)	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
MYALGIA	≤63 Days (All)	204	3 (1%)	1.0000	3	2 (67%)	1 (33%)	0	0
	≤49 Days (Group 1)	145	3 (2%)		3	2 (67%)	1 (33%)	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
SKELETAL PAIN	≤63 Days (All)	204	1 (<1%)	1.0000	1	0	1 (100%)	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	0	1 (100%)	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
CENTR & PERIPH NERVOUS SYSTEM DISORDERS									
ANY EVENT	≤63 Days (All)	204	59 (29%)	0.9684	90	42 (47%)	33 (37%)	15 (17%)	0
	≤49 Days (Group 1)	145	43 (30%)		67	31 (46%)	26 (39%)	10 (15%)	0
	50-56 Days (Group 2)	40	11 (28%)		15	6 (40%)	5 (33%)	4 (27%)	0
	57-63 Days (Group 3)	19	5 (26%)		8	5 (63%)	2 (25%)	1 (13%)	0

[1] Includes all adverse events reported at any point in the study, regardless of causality.
[2] NOS = Not otherwise specified
[3] Gestational age group was assigned by the investigator based upon menstrual history, pelvic examination and vaginal ultrasonography.
[4] Events in this body system occurred during the study blood sampling.
Appendix A.1, Tables 16 and 25

Appendix D, Table [illegible] (Continued)
Adverse Events [1] By Center
[Safety Evaluable Patients]

Center: MISHELL (#1)

Body System/Event [2]	Gestational Age Group [3]	Total Number of Pts	Number of Pts w/Event	Fisher's exact p-value	Number of Events	Severity: Mild	Moderate	Severe	Unknown
CENTR & PERIPH NERVOUS SYSTEM DISORDERS (cont.)									
DIZZINESS	≤63 Days (All)	204	25 (12%)	0.5331	32	16 (50%)	7 (22%)	9 (28%)	0
	≤49 Days (Group 1)	145	19 (13%)		23	12 (52%)	5 (22%)	6 (26%)	0
	50-56 Days (Group 2)	40	3 (8%)		5	2 (40%)	1 (20%)	2 (40%)	0
	57-63 Days (Group 3)	19	3 (16%)		4	2 (50%)	1 (25%)	1 (25%)	0
HEADACHE	≤63 Days (All)	204	39 (19%)	1.0000	56	25 (45%)	26 (46%)	5 (9%)	0
	≤49 Days (Group 1)	145	28 (19%)		42	18 (43%)	21 (50%)	3 (7%)	0
	50-56 Days (Group 2)	40	8 (20%)		10	4 (40%)	4 (40%)	2 (20%)	0
	57-63 Days (Group 3)	19	3 (16%)		4	3 (75%)	1 (25%)	0	0
MIGRAINE	≤63 Days (All)	204	1 (<1%)	1.0000	1	0	0	1 (100%)	0
	≤49 Days (Group 1)	145	1 (<1%)		1	0	0	1 (100%)	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
NEURALGIA	≤63 Days (All)	204	1 (<1%)	1.0000	1	1 (100%)	0	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	1 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
VISION DISORDERS									
ANY EVENT	≤63 Days (All)	204	3 (1%)	1.0000	3	2 (67%)	0	1 (33%)	0
	≤49 Days (Group 1)	145	3 (2%)		3	2 (67%)	0	1 (33%)	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0

[1] Includes all adverse events reported at any point in the study, regardless of causality.
[2] NOS = Not otherwise specified
[3] Gestational age group was assigned by the investigator based upon menstrual history, pelvic examination and vaginal ultrasonography.
[4] Events in this body system occurred during the study blood sampling.

Appendix A.1, Tables 16 and 25

Appendix D, Table 5a (Continued)
Adverse Events [1] By Center
[Safety Evaluable Patients]

Center: MISHELL (#1)

Body System/Event [2]	Gestational Age Group [3]	Total Number of Pts	Number of Pts w/Event	Fisher's exact p-value	Number of Events	Severity: Mild	Moderate	Severe	Unknown
VISION DISORDERS (cont.)									
EYE INFECTION	≤63 Days (All)	204	1 (<1%)	1.0000	1	1 (100%)	0	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	1 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
EYE PAIN	≤63 Days (All)	204	1 (<1%)	1.0000	1	0	0	1 (100%)	0
	≤49 Days (Group 1)	145	1 (<1%)		1	0	0	1 (100%)	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
VISION ABNORMAL	≤63 Days (All)	204	1 (<1%)	1.0000	1	1 (100%)	0	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	1 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
PSYCHIATRIC DISORDERS									
ANY EVENT	≤63 Days (All)	204	7 (3%)	0.4317	9	2 (22%)	7 (78%)	0	0
	≤49 Days (Group 1)	145	7 (5%)		9	2 (22%)	7 (78%)	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
ANXIETY	≤63 Days (All)	204	5 (2%)	0.7478	6	1 (17%)	5 (83%)	0	0
	≤49 Days (Group 1)	145	5 (3%)		6	1 (17%)	5 (83%)	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0

[1] Includes all adverse events reported at any point in the study, regardless of causality.
[2] NOS = Not otherwise specified
[3] Gestational age group was assigned by the investigator based upon menstrual history, pelvic examination and vaginal ultrasonography.
[4] Events in this body system occurred during the study blood sampling.

Appendix A.1, Tables 16 and 25

Appendix D, Table 5a (Continued)
Adverse Events [1] By Center
[Safety Evaluable Patients]

Center: MISHELL (#1)

Body System/Event [2]	Gestational Age Group [3]	Total Number of Pts	Number of Pts w/Event	Fisher's exact p value	Number of Events	Severity: Mild	Moderate	Severe	Unknown
PSYCHIATRIC DISORDERS (cont.)									
DEPRESSION	≤63 Days (All)	204	1 (<1%)	1.0000	1	0	1 (100%)	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	0	1 (100%)	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
INSOMNIA	≤63 Days (All)	204	2 (<1%)	1.0000	2	1 (50%)	1 (50%)	0	0
	≤49 Days (Group 1)	145	2 (1%)		2	1 (50%)	1 (50%)	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
GASTRO-INTESTINAL SYSTEM DISORDERS									
ANY EVENT	≤63 Days (All)	204	140 (69%)	0.8832	349	121 (35%)	90 (26%)	138 (40%)	0
	≤49 Days (Group 1)	145	98 (68%)		224	86 (38%)	51 (23%)	87 (39%)	0
	50-56 Days (Group 2)	40	29 (73%)		87	23 (26%)	27 (31%)	37 (43%)	0
	57-63 Days (Group 3)	19	13 (68%)		38	12 (32%)	12 (32%)	14 (37%)	0
ABDOMINAL PAIN	≤63 Days (All)	204	2 (<1%)	1.0000	2	2 (100%)	0	0	0
	≤49 Days (Group 1)	145	2 (1%)		2	2 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
CONSTIPATION	≤63 Days (All)	204	2 (<1%)	1.0000	2	2 (100%)	0	0	0
	≤49 Days (Group 1)	145	2 (1%)		2	2 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0

[1] Includes all adverse events reported at any point in the study, regardless of causality.
[2] NOS = Not otherwise specified
[3] Gestational age group was assigned by the investigator based upon menstrual history, pelvic examination and vaginal ultrasonography.
[4] Events in this body system occurred during the study blood sampling.

Appendix A.1, Tables 16 and 25

Appendix D, Table 5a (Continued)
Adverse Events [1] By Center
[Safety Evaluable Patients]

Center: MISHELL (#1)

Body System/Event [2]	Gestational Age Group [3]	Total Number of Pts	Number of Pts w/Event	Fisher's exact p-value	Number of Events	Severity: Mild	Moderate	Severe	Unknown
GASTRO-INTESTINAL SYSTEM DISORDERS (cont.)									
DIARRHEA	≤63 Days (All)	204	28 (14%)	0.0780	32	21 (66%)	7 (22%)	4 (13%)	0
	≤49 Days (Group 1)	145	18 (12%)		19	13 (68%)	3 (16%)	3 (16%)	0
	50-56 Days (Group 2)	40	4 (10%)		6	4 (67%)	2 (33%)	0	0
	57-63 Days (Group 3)	19	6 (32%)		7	4 (57%)	2 (29%)	1 (14%)	0
DYSPEPSIA	≤63 Days (All)	204	6 (3%)	0.4929	8	3 (38%)	4 (50%)	1 (13%)	0
	≤49 Days (Group 1)	145	6 (4%)		8	3 (38%)	4 (50%)	1 (13%)	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
FLATULENCE	≤63 Days (All)	204	2 (<1%)	1.0000	2	2 (100%)	0	0	0
	≤49 Days (Group 1)	145	2 (1%)		2	2 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
GASTRIC ULCER	≤63 Days (All)	204	1 (<1%)	0.2892	2	0	2 (100%)	0	0
	≤49 Days (Group 1)	145	0		0	0	0	0	0
	50-56 Days (Group 2)	40	1 (3%)		2	0	2 (100%)	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
HAEMORRHOIDS	≤63 Days (All)	204	1 (<1%)	1.0000	1	1 (100%)	0	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	1 (100%)	0	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0

[1] Includes all adverse events reported at any point in the study, regardless of causality.
[2] NOS = Not otherwise specified
[3] Gestational age group was assigned by the investigator based upon menstrual history, pelvic examination and vaginal ultrasonography.
[4] Events in this body system occurred during the study blood sampling.

Appendix D, Table 5a (Continued)
Adverse Events [1] By Center
[Safety Evaluable, Patients]

Center: MISHELL (#1)

Body System/Event [2]	Gestational Age Group [3]	Total Number of Pts	Number of Pts w/Event	Fisher's exact p-value	Number of Events	Severity: Mild	Moderate	Severe	Unknown
GASTRO-INTESTINAL SYSTEM DISORDERS (cont.)									
NAUSEA	≤63 Days (All)	204	127 (62%)	0.5180	233	73 (31%)	49 (21%)	111 (48%)	0
	≤49 Days (Group 1)	145	87 (60%)		152	55 (36%)	28 (18%)	69 (45%)	0
	50-56 Days (Group 2)	40	28 (70%)		61	14 (23%)	16 (26%)	31 (51%)	0
	57-63 Days (Group 3)	19	12 (63%)		20	4 (20%)	5 (25%)	11 (55%)	0
VOMITING	≤63 Days (All)	204	46 (23%)	0.3365	67	17 (25%)	28 (42%)	22 (33%)	0
	≤49 Days (Group 1)	145	29 (20%)		38	8 (21%)	16 (42%)	14 (37%)	0
	50-56 Days (Group 2)	40	11 (28%)		18	5 (28%)	7 (39%)	6 (33%)	0
	57-63 Days (Group 3)	19	6 (32%)		11	4 (36%)	5 (45%)	2 (18%)	0
METABOLIC AND NUTRITIONAL DISORDERS									
ANY EVENT	≤63 Days (All)	204	4 (2%)	1.0000	4	1 (25%)	1 (25%)	2 (50%)	0
	≤49 Days (Group 1)	145	3 (2%)		3	1 (33%)	1 (33%)	1 (33%)	0
	50-56 Days (Group 2)	40	1 (3%)		1	0	0	1 (100%)	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
DEHYDRATION	≤63 Days (All)	204	3 (1%)	0.6431	3	1 (33%)	0	2 (67%)	0
	≤49 Days (Group 1)	145	2 (1%)		2	1 (50%)	0	1 (50%)	0
	50-56 Days (Group 2)	40	1 (3%)		1	0	0	1 (100%)	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0
HYPOGLYCAEMIA	≤63 Days (All)	204	1 (<1%)	1.0000	1	0	1 (100%)	0	0
	≤49 Days (Group 1)	145	1 (<1%)		1	0	1 (100%)	0	0
	50-56 Days (Group 2)	40	0		0	0	0	0	0
	57-63 Days (Group 3)	19	0		0	0	0	0	0

[1] Includes all adverse events reported at any point in the study, regardless of causality.
[2] NOS = Not otherwise specified
[3] Gestational age group was assigned by the investigator based upon menstrual history, pelvic examination and vaginal ultrasonography.
[4] Events in this body system occurred during the study blood sampling.

Appendix A.1, Tables 16 and 25