CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-687

STATISTICAL REVIEW(S)

FEB 1 4 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Statistical Reviewer

TO: NDA 20-687

SUBJECT: Statistical comments on Amendment 024

A statistical evaluation of the European studies was completed previously. The clinical results of the supporting U.S. studies that are in amendment 024 are similar enough to the results of the European studies that, in the opinion of the medical reviewer, a statistical evaluation of the results of the U.S. studies is not required.

/S/
2/14/00

cc:
Archival NDA 20-687

APPEARS THIS WAY
ON ORIGINAL

MAY 2 1 1996

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-687/Drug Class: 1P

APPLICANT: The Population Council

NAME OF DRUG: Mifepristone

INDICATION: Medical Termination of Intrauterine Pregnancy through 49 Days' Gestational Age

DOCUMENTS REVIEWED: Volumes 1.1, 1.94-1.117 of NDA 20-687 dated March 14, 1996

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer,

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. The sponsor is seeking an indication for patients with amenorrhea of 49 days or less who request a voluntary termination of pregnancy based on the results of two French open-label multi-center studies.

2. The complete expulsion rates in the proposed patient population were 95% and 99% in Studies FFR/91/486/14 and FF/92/486/24 respectively. In the absence of a concurrent control group in each of these studies, it is a matter of clinical judgement as to whether or not the proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy.

3. The most common adverse events were painful contractions of the uterus, nausea, vomiting, and diarrhea.

4. FDA clinicians should address the validity of the sponsor's France-U.S. patient comparability assumption.

KEY WORDS: abortion, amenorrhea, aspiration, diarrhea, expulsion, french, gestational, intrauterine pregnancy, mifepristone, misoprostol, multi-center, nausea, open-label, painful contractions, ultrasound, uterus, vomiting, worst-case

BACKGROUND

The Population Council has submitted the results of two French open-label multi-center studies. The sponsor claims that the results of these studies support the approval of mifepristone and a single dose of misoprostol in patients with amenorrhea of 49 days or less who request a voluntary termination of pregnancy.

A proposal to extend the indication to patients with amenorrhea up to 63 days will be supported by the results of two U.S. clinical studies which are to be submitted at a later date.

The remainder of this review will discuss the results of the above mentioned French studies.

STUDY FFR/91/486/14

This open-label multi-center (24 centers) study was conducted in France "to evaluate the efficacy, tolerance, and safety of 600mg mifepristone followed by .4mg misoprostol 48 hours later for the termination of pregnancy in women whose duration of amenorrhea was no more than 49 days."

Women who requested a voluntary termination of pregnancy, who were familiar with the legal steps required in France to obtain the procedure and who satisfied all study inclusion and exclusion criteria were eligible to participate.

Gestational age was to be verified as no more than 49 days, based on the number of days from the onset of the last menstrual period. At the discretion of the examining physician, and/or in cases where there was a question as to the patient's duration of amenorrhea, an ultrasound examination was to be performed to determine gestational age.

Since the ultrasound estimate of gestational age was more reliable than the patient's estimate based on her recollection of the date of the first day of her last menstrual period, gestational age based on the ultrasound examination was used if available. If one was not performed, the estimate of gestational age was based on the patient's estimate.

All patients were administered (Day 1) three 200mg mifepristone tablets by mouth, in the presence of a study investigator on the first day of the study. Patients were then instructed to return approximately 48 hours (Day 3) subsequent to the administration of mifepristone.

On Day 3, patients were administered two .2mg misoprostol tablets by mouth in the presence of the study investigator if expulsion had not already occurred. Patients remained at the clinic under observation for at least four hours subsequent to the administration of misoprostol. Patients were then given an appointment to return to the clinic 8 to 15 days later for a final assessment of the pregnancy termination procedure.

Treatment outcome was assessed categorically at the final assessment appointment as follows for each patient:

1. complete expulsion
2. incomplete expulsion
3. ongoing pregnancy
4. surgical procedure for bleeding.

A patient who experienced a complete expulsion was classified as a treatment success whereas all other assessed patients were considered to be treatment failures.

The primary efficacy parameter was the proportion of patients who experienced a complete expulsion (treatment success).

REVIEWER'S COMMENTS ON STUDY FFR/91/486/14

A total of 1286 patients were enrolled and treated with mifepristone as described above. All patients were included in the sponsor's safety analyses. However, 81 patients were excluded from the sponsor's efficacy analyses. Sixty-nine of these patients were excluded since neither an ultrasound examination nor an hCG B subunit pregnancy test was performed to confirm pregnancy.

The success rate (Table 1) for the sponsor's efficacy population was 95.4% as 1149 of the 1205 efficacy population patients experienced a complete expulsion. Thirty-five of these patients were determined to have had a complete expulsion at the Day 3 clinical visit and consequently were not administered misoprostol. An additional 26 patients also had a complete expulsion prior to receiving misoprostol but this was not determined until after misoprostol was administered.

The success rate ranged from 85% to 100% across centers as 13 of the 24 centers experienced at least a 95% success rate.

Table 2 displays the success rate by gestational age. In examining this table, one notes that there was a statistically significant ($p = .01$) inverse relationship between gestational age and the success rate as the success rate generally declined with increasing gestational age.

In examining Table 2, one also notes that 16 of the efficacy population patients had a gestational age, greater than 49 days. This is due to the fact that investigators enrolled patients with durations of amenorrhea which exceeded 49 days in violation of the study protocol inclusion criteria.

If one excludes the above mentioned 16 efficacy population patients, one notes (Table 2) that the success rate for the efficacy population patients whose gestational age did not exceed 49 days was also 95.4% (1134/1189). The corresponding 95% success rate confidence interval is (94.2%,

96.6%).

In examining the treatment outcome data provided by the sponsor for the 81 patients that were excluded from the sponsor's efficacy analyses, this reviewer noted that 75 of these patients had a gestational age that did not exceed 49 days. The gestational age was not determined for two patients (both successes) and the gestational age for the remaining 4 patients (3 successes) exceeded 49 days.

The treatment outcome for 48 of the above mentioned 75 patients was not determined. Twenty-six of the remaining 27 patients experienced a complete expulsion as the only treatment failure was due to a surgical procedure for bleeding.

If one includes these 27 assessed patients with the above mentioned 1189 efficacy population patients whose gestational age did not exceed 49 days, the success rate remains 95.4% (1160/1216).

Each of the 48 patients whose treatment outcome was not assessed had a gestational age that did not exceed 49 days. If one considers each of these patients to be a treatment failure (worst-case analysis) then the overall success rate for patients whose gestational age did not exceed 49 days would be 91.8% (1160/1264). The corresponding worst-case 95% success rate confidence interval is (90.3%, 93.3%).

A total of 1104 patients (85.8%) reported at least one adverse event. There were no deaths and no patient was discontinued from the study due to an adverse event.

Table 3 displays the adverse events which were reported by at least 1% of the patient population. In examining this table, one notes that the most common adverse events were painful contractions of the uterus, nausea, vomiting, and diarrhea.

STUDY FF/92/486/24

This open-label multi-center (11 centers) study was conducted in France "to evaluate the efficacy, tolerance, and safety of mifepristone and misoprostol for the termination of pregnancies of no more than 63 days from onset of the last menstrual period."

Women who requested a voluntary termination of pregnancy, who were familiar with the legal steps required in France to obtain the procedure and who satisfied all study inclusion and exclusion criteria were eligible to participate.

Gestational age was to be verified as no more than 63 days based on the number of days from the onset of the last menstrual period. At the discretion of the examining physician, and/or in cases where there was a question as to the patient's duration of amenorrhea and/or whether the pregnancy was intrauterine, an ultrasound examination of the uterus was to be performed.

Since the ultrasound estimate of gestational age was more reliable than the patient's estimate based on her recollection of the date of the first day of her last menstrual period, gestational age based on the ultrasound examination was used if available. If one was not performed, the estimate of gestational age was based on the patient's estimate.

All patients were administered (Day 1) three 200mg mifepristone tablets by mouth, in the presence of a study investigator on the first day of the study. Patients were then instructed to return 36-48 hours (Day 3) subsequent to the administration of mifepristone.

On Day 3, patients were administered two .2mg misoprostol tablets by mouth in the presence of the study investigator if expulsion had not already occurred. Patients remained at the clinic under observation for at least four hours subsequent to the administration of misoprostol. However, in contrast to Study FFR/91/486/14, if complete expulsion had not occurred during the first 3 hours of the 4 hour observation period, patients were to receive an additional .2mg misoprostol tablet and were to remain under observation for an additional 2 hours. Consequently, patients who received the additional .2mg misoprostol tablet were under observation for a total of 5 hours.

All patients, subsequent to the 4-5 hour observation period were then given an appointment to return to the clinic between Days 10 and 18 for a final assessment of the pregnancy termination procedure.

As in Study FFR/91/486/14, treatment outcome was assessed categorically at the final assessment appointment as follows for each patient:

1. complete expulsion
2. incomplete expulsion
3. ongoing pregnancy
4. surgical procedure for bleeding.

A patient who experienced a complete expulsion was classified as a treatment success whereas all other assessed patients were considered to be treatment failures.

The primary efficacy parameter, as in Study FFR/91/486/14, was the proportion of patients who experienced a complete expulsion (treatment success).

REVIEWER'S COMMENTS ON STUDY FF/92/486/24

A total of 1194 patients were enrolled and treated with mifepristone as described above. All patients were included in the sponsor's safety analyses. However, 90 patients were excluded from the sponsor's efficacy analyses. Eighty-two of these patients were excluded since neither an ultrasound examination nor an hCG B subunit pregnancy test was performed to confirm pregnancy.

The success rate (Table 4) for the sponsor's efficacy population was 92.8% as 1025 of the 1104 efficacy population patients experienced a complete expulsion. Misoprostol was not administered to 27 of these patients at the Day 3 clinical visit. Twenty-six of these patients were determined to have had a complete expulsion whereas the remaining patient had an incomplete expulsion. An additional 13 patients also had a complete expulsion prior to receiving misoprostol but this was not determined until after misoprostol was administered.

The success rate ranged from 82.9% to 97.5% across centers as 9 of the 11 centers experienced at least a 90% success rate.

Table 5 displays the success rate by gestational age. In examining this table, one notes that there was a statistically significant ($p < .001$) inverse relationship between gestational age and the success rate as the success rate generally declined with increasing gestational age.

The sponsor's proposed labeling (indication and usage section) states that mifepristone "is indicated for the medical termination of intrauterine pregnancy through 49 days' gestational age." In examining Table 5, one notes that the success rate for this portion of the sponsor's efficacy population is 95.7% which is very similar to the corresponding Study FFR/91/486/14 efficacy population success rate of 95.4% which is displayed in Table 2.

The sponsor's proposed labeling (dosage and administration section) states that "unless abortion has occurred and is confirmed by clinical examination or ultrasonographic scan, the patient must take two .2mg tablets of misoprostol two days after ingesting mifepristone." There is no reference in the sponsor's proposed labeling to the administration of a third .2mg misoprostol tablet as was accomplished in this study.

Consequently, in the opinion of this reviewer, one should focus on those patients whose gestational age did not exceed 49 days and who took at most two misoprostol .2mg tablets on Day 3 of the study to determine if the results of this study support those of Study FFR/91/486/14 for the sponsor's proposed patient population. In doing so, this reviewer noted that 210 patients in the sponsor's efficacy population satisfied these criteria and that 208 of these patients experienced a complete expulsion for a success rate of 99.0%.

In examining the treatment outcome data provided by the sponsor for the 90 patients that were excluded from the sponsor's efficacy analyses, this reviewer noted that 29 of these patients had a gestational age, that did not exceed 49 days and did not take more than two .2mg misoprostol tablets.

The treatment outcome for 9 of the above mentioned 29 patients was not determined. Nineteen of the remaining 20 patients experienced a complete expulsion as the only treatment failure was due to an ongoing pregnancy.

If one includes these 20 patients with the above mentioned 210 efficacy population patients who

satisfied the gestational age and misoprostol labeling criteria, one obtains a success rate of 98.7% (227/230). A worst-case analysis in which the 9 patients whose treatment outcome was not determined are classified as treatment failures yields a success rate of 95.0% (227/239).

A total of 1108 patients (92.8%) reported at least one adverse event. There were no deaths and no patient was discontinued from the study due to an adverse event.

Table 6 displays the adverse events which were reported by at least 1% of the patient population. In examining this table, one notes that as in Study FFR/91/486/14, (Table 3) the most common adverse events were painful contractions of the uterus, nausea, vomiting, and diarrhea.

REVIEWER'S CONCLUDING COMMENTS

The Population Council has submitted the results of two French open-label multi-center studies to support the approval of mifepristone and a single dose of misoprostol in patients with amenorrhea of 49 days or less who request a voluntary termination of pregnancy.

The complete expulsion (success) rate experienced by the sponsor's Study FFR/91/486/14 efficacy population patients who satisfied the 49 day-single misoprostol dose criteria was 95.4% (Table 7, Category E). The corresponding success rate for all such patients with a known treatment outcome was also 95.4% (Table 7, Category F).

These results based on the experience of approximately 1200 patients are supported by the results based on the experience of the approximately 200 Study FF/92/486/24 patients who satisfied the 49 day single-misoprostol dose criteria (Table 7, Category E: 99.0%, Category F: 98.7%).

Worst-case analyses in which patients with an undetermined treatment outcome were considered treatment failures yielded success rates (Table 7, Category G) of 91.8% and 95.0% in Studies FFR/91/486/14 and FF/92/486/24 respectively.

The most common adverse events in each study were painful contractions of the uterus, nausea, vomiting, and diarrhea.

The sponsor considered the French data to be comparable to data which would be obtained if comparable trials were conducted in the U.S. by U.S. investigators. In noting that the population studied was predominately caucasian by ethnic origin, the sponsor stated that the population was representative of the racial and ethnic diversity of France and that gynecological and obstetric practice patterns do not differ significantly between France and the United States.

The FDA clinicians should comment on the validity of the sponsor's U.S.-France patient comparability assumption.

In the absence of a concurrent control group in each of these studies, it is a matter of clinical

judgement whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy.

[redacted] /S/

Concur: [redacted] /S/ 5-21-96

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Archival NDA 20-687

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Chron.

This review consists of 8 pages of text and 7 pages of tables.

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ON ORIGINAL

TABLE 1
STUDY FFR/91/486/14

TREATMENT OUTCOME (EFFICACY POPULATION)

OUTCOME	N	PERCENTAGE	CLASSIFICATION
Complete Expulsion	1149	95.4	Success
Incomplete Expulsion	34	2.8	Failure
Ongoing Pregnancy	18	1.5	Failure
Surgical Procedure for Bleeding	4	.3	Failure
Total	1205		

+ 95% confidence interval: (94.2%, 96.6%)

TABLE 2
STUDY FFR/91/486/14

SUCCESS RATE BY GESTATIONAL AGE
EFFICACY POPULATION

GESTATIONAL AGE (DAYS)	SUCCESS RATE
< 36	117/119 (98.3%)
36 - 42	447/463 (98.5%)
43 - 49	570/607 (93.9%)
50 - 56	12/13 (92.3%)
57 - 63	3/3 (100.0%)
	p = .01*
< = 49 #	1134/1189 (95.4%)

* There was a statistically significant inverse relationship between gestational age and the success rate.

\# Only patients who satisfied the protocol gestational age criterion.

TABLE 3
STUDY FFR/91/486/14

ADVERSE EVENTS
(AT LEAST A 1% INCIDENCE)

ADVERSE EVENT	FREQUENCY (N = 1286)	PERCENTAGE
Painful Contraction of Uterus	1010	78.5
Nausea	533	40.7
Vomiting	216	16.8
Diarrhea	158	12.3
Headache	34	2.6
Fainting	25	1.9
Dizziness	15	1.2
Pelvic Pain	15	1.2
Uterine Pain	15	1.2
Asthenia	14	1.1

TABLE 4
STUDY FF/92/486/24

TREATMENT OUTCOME (EFFICACY POPULATION)

OUTCOME	N	PERCENTAGE	CLASSIFICATION
Complete Expulsion	1025	92.8	Success*
Incomplete Expulsion	44	4.0	Failure
Ongoing Pregnancy	25	2.3	Failure
Surgical Procedure for Bleeding	10	.9	Failure
Total	1104	[illegible]	[illegible]

* 95% confidence interval: (91.3%, 94.3%)

TABLE 5
STUDY FF/92/486/24

SUCCESS RATE BY GESTATIONAL AGE
EFFICACY POPULATION

GESTATIONAL AGE (DAYS)	SUCCESS RATE
< 36	15/15 (100.0%)
36 - 42	163/171 (95.3%)
43 - 49	293/306 (95.8%)
50 - 56	358/389 (92.0%)
57 - 63	196/223 (87.9%)
	$p \leq .001$*
< = 49 #	471/492 (95.7%)

* There was a statistically significant inverse relationship between gestational age and the success rate.

\# Only patients who gestational age did not exceed 49 days.

TABLE 6
STUDY FF/92/486/24

ADVERSE EVENTS
(AT LEAST A 1% INCIDENCE)

ADVERSE EVENT	FREQUENCY (N = 1194)	PERCENTAGE
Painful Contraction of Uterus	1022	85.6
Nausea	596	49.9
Vomiting	348	29.1
Diarrhea	184	15.4
Pelvic Pain	86	7.2
Pelvic Spasm	49	4.1
Metrorrhagia	40	3.4
Headache	37	3.1
Anemia	35	2.9
Dizziness	31	2.6
Asthenia	19	1.6
Abdominal Pain	19	1.6
Fainting	18	1.5

TABLE 7
SUCCESS RATE (COMPLETE EXPULSION) RATES

CATEGORY +	FFR/91/486/14	FF/92/486/24
A	1286	1194
B	1205	1104
C	1149/1205 (95.4%)	1025/1104 (92.8%)
D	1134/1189 (95.4%)	471/492 (95.7%)
E	1134/1189 (95.4%)	208/210 (99.0%)
F	1160/1216 (95.4%)	227/230 (98.7%)
G	1160/1264 (91.8%)	227/239 (95.0%)

±

A Number of patients enrolled.

B Number of patients in sponsor's efficacy population.

C Success rate in sponsor's efficacy population.

D Success rate in sponsor's efficacy population for patients whose gestational age did not exceed 49 days.

E Success rate in sponsor's efficacy population for patients whose gestational age did not exceed 49 days and who took at most two .2mg misoprostol tablets.

F Success rate in all patients with a known treatment outcome whose gestational age did not exceed 49 days and who took at most two .2mg misoprostol tablets.

G Worst-case success rate in all patients whose gestational age did not exceed 49 days and who took at most two .2mg misoprostol tablets. Patients with an unknown treatment outcome were assumed to be treatment failures.