CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-756

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

Date: 5/7/97

NDA #: 20-756

Applicant: Columbia Research Labs

Name of Drug: Crinone (progesterone gel)

Indication: For progesterone supplementation or replacement as part of an ART treatment for infertile women with documented or suspected progesterone deficiency.

Documents Reviewed: Vol. 1.01, .1.04-1.10

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Ridgely Bennett. M.D. (HFD-580)

Summary of Studies

Study #007US was a randomized, open-label, single-center clinical trial for the indication of initiating and maintaining pregnancies in women undergoing ART procedures. The subjects in this study were women, ages 18-50, with either partial ovarian function or premature ovarian failure who were receiving a donor egg transfer. The single center is the Jones Institute for Reproductive Medicine in the U.S.

Study #F01 was a randomized, open-label, multicenter trial conducted in 7 centers in Europe. The subjects were women, ages 22-41, with tubal, idiopathic, or endometriosis-linked sterility, and normal ovulatory cycles, who had an embryo transfer as part of an IVF procedure. All women received a GnRH analogue to suppress endogenous progesterone. The goal of this study was to provide evidence for Crinone in the support of the luteal phase of pregnancy in patients undergoing an IVF procedure. It is included in NDA 20-756 as a supportive study.

The studies were different in several respects:

- The cause of infertility among subjects in 007US was related to no or reduced endogenous progesterone, while the cause of infertility among subjects in study F01 was tubal, idiopathic, or endometriosis-linked sterility.
- In study 007US an unspecified ART procedure was performed with a donor egg transfer; in study F01 the ART procedure was IVF with patient's eggs.
- The treatment regimens and duration of treatment (see Table 1) differ in the 2 studies.
- Study 007US included only a single center; study F01 included 6 centers.
- The mean age for the Crinone group was 39.9 in study 007US and 31.8 in study F01.
- The daily dose in study 007US was 90 mg twice a day; in study F01 the daily dose was 90 mg once a day.

Table 1: Summary of Randomized, Controlled, Open-label Studies

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
COL-1620-007US (8/94 - 6/96)	1 (U.S.)	COL-1620 90 mg b.i.d (n=64) IM Progesterone 100 mg daily (n=23)	no treatment group comparisons to the active-control group	randomized open-label 2 treatment arms	up to 18-20 weeks (3 cycles: pilot - up to 34 days DE - up to 34 days 10-week trmt cycle if chem. preg.)
COL-1620-F01 (3/93 - 5/94)	6 (all non-U.S.)	COL-1620 90 mg daily (n=139) Utrogestan 100 300 mg daily (n=144)	active-control	randomized open-label 2 treatment arms	up to 30 days (trmt. for 14 days after embryo transfer, then addl. 16 days if chemical preg.)

STUDY # 1620-COL-007US

Background

Study # 1620-COL-007US (007US) was a randomized, open-label, single-center clinical trial. An active-control treatment, IM progesterone, was included in the study only to provide evidence for an assumed (historical) success rate. The results for the IM progesterone treatment group were not used as a comparator for the Crinone treatment group. The progesterone study treatment was given in a regimen which included estradiol (Estraderm) for all patients and a pituitary suppressant (Lupron) only for those patients with partial ovarian function.

The sample consisted of women ages 18-50 years with premature ovarian failure or partial ovarian function who were undergoing donor egg (DE) transfer as a means to get pregnant. Donor egg transfer is a procedure used in advanced reproductive technology (ART). Up to 100 subjects were to be randomized to the 2 treatment groups after a screening visit. The first 10 subjects were randomized equally to the 2 treatment groups, with the remaining subjects randomly assigned by a 7:3 ratio to the Crinone and IM progesterone treatment groups to achieve up to 68 subjects in the Crinone group and up to 32 subjects in the IM progesterone group. When a total of 60 subjects had received a donor egg, enrollment of new subjects into the study would end.

Study 007US included 3 stages: Pilot Cycle, Donor Egg Cycle, and Ten-week Treatment Cycle. Subjects received the progesterone treatment during all 3 cycles. The goal of the pilot cycle was to assure that the administration of estradiol and progesterone would adequately prime the endometrium to receive the donor egg. Subjects who did not have sufficiently primed endometria after the pilot cycle were discontinued from the study. The donor egg cycle was the same as the pilot cycle, except the donor egg transfer was actually performed. If a subject was diagnosed as being chemically pregnant at the end of the donor egg cycle, she continued with the assigned progesterone treatment in the 10-week treatment cycle. If, during the 10-week treatment period, a woman's pregnancy ended, treatment with the progesterone was discontinued. The treatment regimens for women with partial ovarian function and those with premature ovarian failure were identical in the 3 cycles, but those with partial ovarian failure also under went a Pre-Pilot Cycle and a Pre-Donor Egg Cycle at which time they were administered Lupron to suppress remaining ovarian function.

The goal of study 007US was to evaluate the effectiveness of Crinone in initiating (chemical) and maintaining (clinical and ongoing) pregnancies in women undergoing ART. To study progesterone supplementation in ART in the most extreme situation, the study tested the efficacy of Crinone in donor egg recipients in whom no endogenous source of progesterone exists.

Primary variables of interest are:

Variable	Time point
Chemical pregnancy rate (% transfer)	day 28-34 of gestation = 11-17 days after DE transfer
Clinical pregnancy rate (% transfer)	5^{th} - 6^{th} wk of gestation (during 10-wk trmt cycle)
On-going pregnancy rate (% transfer)	24^{th} wk of gestation (after 10-wk trmt cycle)

Gestation is defined as starting on the first day of the DE cycle; DE transfer was done on day 17 of the DE cycle.

The secondary variable of interest is:

Variable	Time point
Delivery rate (% transfer)	completion of pregnancy

A total of 99 patients were randomized to the two treatment groups. The two groups were similar with regard to most of the demographic characteristics at baseline, as shown in Table 2. Differences did exist in the distribution of subjects across race and age categories.

- The Crinone treatment group had 9 (13.2%) non-Caucasian subjects, but the IM progesterone treatment group had only one (3.2%) non-Caucasian subject.

- The mean and median age were similar for the 2 treatment groups, but the distribution by age categories shows that the Crinone group had 12 subjects (17.6%) who were age 45 and above, while the IM progesterone group had only 1 subject (3.2%) age 45 and above.

Table 2: Demographic characteristics (Study #007US)

	Crinone (n=68)		IM Progesterone (n=31)	
Characteristic	Mean	S.D.	Mean	S.D.
Age (years)	39.9	4.8	39.3	4.1
Weight (lbs)	138.5	24.8	136.9	22.2
Height (inches)	64.2	2.8	64.7	2.4
	Median		Median	
Age (years)	41		40	
	n	%	n	%
Ovarian Function				
Partial Ovarian Function	58	85.3	26	83.9
Premature Ovarian Failure	10	14.7	5	16.1
Race				
Caucasian	59	86.8	30	96.8
Other	9	13.2	1	3.2
Age categories (years)				
<30	2	2.9	1	3.2
30-34	9	13.2	4	12.9
35-39	15	22.1	9	29.0
40-44	30	44.1	16	51.6
≥45	12	17.6	1	3.2

The disposition of the subjects was not similar across the 2 treatment groups. In the IM progesterone treatment group, 45.2% of the subjects had dropped or were discontinued prior to receiving the Donor Egg transfer, while only 20.6% of the subjects in the Crinone treatment group had dropped from the study at that stage. The greater proportion of subjects in the Crinone treatment group continuing to the 10-week treatment cycle reflects the imbalance in the treatment groups at the DE transfer stage.

Between the start of the Pilot cycle and the start of the DE transfer cycle, 22.5% of the subjects in the IM Progesterone group discontinued, versus only 10.3% dropped from the Crinone group. This raises concerns that the subjects remaining in the 2 treatment groups may not be similar at the DE transfer cycle stage, thus introducing bias which randomization is intended to prevent. Fortunately, in this study, the 2 treatment groups are not being compared in the analyses, so the possible bias does not impact the conclusions reached.

Among the subjects who discontinued from the IM progesterone treatment group prior to DE transfer, Subject Desire was given as the reason by 6 of the 13, with 2 subjects specifically mentioning inability to self-administer the injections.

Table 3: Disposition of subjects by group (Study #007US)

	Crinone		IM Progesterone	
	n	rand. %	n	rand. %
Randomized	68	100.0	31	100.0
Began Pilot Cycle	61	89.7	25	80.6
Began DE Cycle	54	79.4	18	58.1
Received Donor Egg Transfer (while taking study treatment) *	54	79.4	17	54.8
Began 10-week treatment Cycle	26	38.2	6	19.4

Source: Vol. 1.04, Table 1.0 and Safety Update Table 7.0

* One subject in the IM progesterone group received a donor egg but was not receiving study treatment during the transfer cycle due to an allergic reaction to the IM progesterone treatment.

Table 4: Reasons for Discontinuation (Study #007US)

	Crinone		IM Progesterone	
	n	% rand.	n	% rand.
Before Pilot Cycle				
6 Month time limit *	4	5.9	1	3.2
Subject desire	1	1.5	4	12.9
Pregnant	2	2.9	1	3.2
After Pilot / Before DE Cycle				
Protocol violation	2	2.9	1	3.2
Inadequate endometrium	4	5.9	1	3.2
Subject desire	1	1.5	2	6.5
Other	0	0.0	3	9.7
After DE / Before 10-week Treatment Cycle				
No chemical pregnancy	25	36.8	11	35.5
No clinical pregnancy	3	4.4	0	0.0

Source: Vol. 1.04, Tables 1.0, 2.0 and Safety Update Tables 7.0, 8.0

* Failure to start the Pilot cycle within 6 months of screening was a protocol violation.

Applicant's Analysis

The applicant's analysis for the efficacy variables included only subjects who had received a Donor Egg transfer and were receiving the study treatment at the time of transfer. The Medical Officer agrees with this definition of the efficacy population, so the same group of subjects will be used for the analyses considered here.

In the applicant's analysis, only summaries by treatment group were done. The results are given in Table 5a below. Comparison between the two treatment groups was not done by the applicant because the IM progesterone treatment group was included only for summarization and not for statistical tests of comparisons (Protocol, Vol 1.04, pg. 122).

As stated in the protocol (Vol. 1.04), the investigator assumed clinical pregnancy rates of 37% with IM progesterone based on historical experience. Then, for purposes only of calculating a sample size, it was supposed that the clinical pregnancy rate would be reduced by half (18%) without progesterone treatment. Based on these values, a clinical pregnancy rate of 25% was defined as clinically meaningful. The applicant's intent was to compare the results of the Crinone treatment group to the historical experience for the IM progesterone treatment regimen, not to the IM progesterone treatment group in the current study. The IM treatment group in this study was intended to provide supporting evidence for the historical values.

Based on the clinical pregnancy rate result of 48.1% from the Crinone treatment group, the applicant concluded that Crinone, together with continuous estrogen administration, was effective in priming endometrial receptivity and in initiating and maintaining pregnancy in women undergoing donor egg transfer cycles. The applicant also stated that it can be inferred from these results obtained in the worst possible scenario (no endogenous production of progesterone) that Crinone can also suffice in providing progesterone supplementation in all forms of ART when partial and/or relative progesterone insufficiency is documented and/or suspected. (Vol. 1.04, page 57).

Table 5a: Applicant's Results (subjects who received DE transfer while receiving treatment): (Study #007US)

	Crinone		IM Progesterone	
	n	% of DE Transfers	n	% of DE Transfers
Number of subjects	54	100.0	17	100.0
Primary Variables				
Chemical Pregnancy Rate	29	53.7	6	35.3
Clinical Pregnancy Rate	26	48.1	5	29.4
On-going Pregnancy Rate	17	31.5	4	23.5
Secondary Variable				
Delivery Rate	17	31.5	3 *	17.6 *

Source: Vol. 1.04, Panel E, Table 14.1 and Safety Update Tables 20.0, 20.1

* One subject in the IM progesterone group had an ongoing pregnancy as of 2/15/97; delivery results not known.

Reviewer's Analysis

The historical values which the applicant used for comparison to the Crinone results were not documented. Of particular interest to this reviewer would have been the ability to breakdown results with regard to ovarian function status (endogenous production of progesterone), and age. Without this information, the validity of the applicant's comparisons and conclusions is not known.

Comparisons of the results between the 2 treatment groups in the current study was not reasonable because the sample size for the IM progesterone treatment group (n=17) was too small to make adequate conclusions.

Discussions with the Medical Officers concluded that, for women with no endogenous (or medically suppressed) production of progesterone, the pregnancy rate would be zero without progesterone supplementation. Therefore, it was decided that a reasonable assessment of the efficacy for the Crinone treatment would be confidence intervals on the observed pregnancy rates for the Crinone treatment group only. A confidence interval for the primary efficacy variable, clinical pregnancy, which excluded the value zero would be viewed as indicating efficacy. Confidence intervals for the additional pregnancy variables excluding zero would be considered as further support of the efficacy of Crinone in initiating and maintaining pregnancy in women who have no endogenous production of progesterone who are undergoing donor egg transfers.

Table 5b below shows the 95% confidence intervals for the pregnancy rate variables for the Crinone treatment group. The confidence intervals for the 3 pregnancy rate variables all exclude the clinically meaningful rate of zero. This agrees with the applicant's conclusion that Crinone is effective in initiating and maintaining pregnancy in women undergoing DE transfer who have no endogenous production of progesterone.

Table 5b: Reviewer's Results (subjects who received DE transfer while receiving treatment): (Study #007US)

	Crinone			
	n	% of DE Transfers	Lower 95% Confidence Bound	Upper 95% Confidence Bound
Number of subjects	54	100.0		
Primary Variables				
Chemical Pregnancy Rate	29	53.7	40.4	67.0
Clinical Pregnancy Rate	26	48.1	34.8	61.5
On-going Pregnancy Rate	17	31.5	19.1	43.9
Secondary Variable				
Delivery Rate	17	31.5	19.1	43.9

The efficacy population was defined as subjects who had received a Donor Egg transfer and were receiving the study treatment at the time of the transfer. This efficacy population is not the true intent-to-treat population of all subjects randomized to treatment. Without follow-up information on subjects who discontinued, the assumption is that no pregnancies occurred for those subjects. Thus, the results for the intent-to-treat population (Table 5c) include all randomized subjects in the number of subjects, but no additional pregnancies versus the efficacy population. The pregnancy rates are lower than in the efficacy population. as expected, but the confidence intervals still exclude zero. Thus these results do not contradict the results from the analysis with the efficacy population.

Table 5C: Reviewer's Results (all subjects randomized to treatment): (Study #007US)

	Crinone			
	n	% of DE Transfers	Lower 95% Confidence Bound	Upper 95% Confidence Bound
Number of subjects	68	100.0		
Primary Variables				
Chemical Pregnancy Rate	29	42.6	30.9	54.4
Clinical Pregnancy Rate	26	38.2	26.7	49.8
On-going Pregnancy Rate	17	25.0	14.7	35.3
Secondary Variable				
Delivery Rate	17	25.0	14.7	35.3

Subgroup Analyses

For descriptive purposes only, this reviewer compared the primary efficacy results for each treatment group by age group and ovarian function. There was no significant relationship between age group and ovarian function (Fisher's Exact test p-value=1.00).

Age Group Comparison

The age group categories used for this were based on the mean, which was just under 40 for both treatment groups. In the Crinone treatment group, there was a negative association between age and pregnancy rates. The sample size in the IM progesterone group is too small to make any conclusions.

Table 6a:Age Group Comparisons (Study #007US)

	Crinone n=54		IM Progesterone n=17	
	Age 39 and under	Age 40 and older	Age 39 and under	Age 40 and older
Number of subjects	24	30	4	13
Primary Variables				
Chemical Pregnancy Rate (%)	15 (62.5)	14 (46.7)	0 (0.0)	6 (46.2)
Clinical Pregnancy Rate (%)	14 (58.3)	12 (40.0)	0 (0.0)	5 (38.5)
On-going Pregnancy Rate (%)	11 (45.8)	6 (20.0)	0 (0.0)	4 (30.8)
Secondary Variable				
Delivery Rate (%)	11 (45.8)	6 (20.0)	0 (0.0)	3 (23.1) *

* One subject in the IM progesterone group had an ongoing pregnancy as of 2/15/97; delivery results not known.

Ovarian Status Comparison

Women with partial ovarian failure received a different treatment regimen than those with premature ovarian failure. The Pilot Cycle, Donor Egg Cycle, and 10-week Treatment Cycle applied to all subjects. Women with partial ovarian failure also underwent a Pre-Pilot Cycle and a Pre-Donor Egg Cycle at which time they were administered Lupron to suppress remaining ovarian function.

The sample sizes for the subgroups were too small to make comparisons or reach conclusions.

Table 6b:Ovarian Function Category Comparisons (Study #007US)

	Crinone n=54		IM Progesterone n=17	
	Premature Ovarian Failure	Partial Ovarian Function	Premature Ovarian Failure	Partial Ovarian Function
Number of subjects	8	46	2	15
Primary Variables				
Chemical Pregnancy Rate (%)	5 (62.5)	24 (52.2)	0 (0.0)	6 (40.0)
Clinical Pregnancy Rate (%)	4 (50.0)	22 (47.8)	0 (0.0)	5 (33.3)
On-going Pregnancy Rate (%)	3 (37.5)	14 (30.4)	0 (0.0)	4 (26.7)
Secondary Variable				
Delivery Rate (%)	3 (37.5)	14 (30.4)	0 (0.0)	3 (20.0) *

* One subject in the IM progesterone group had an ongoing pregnancy as of 2/15/97; delivery results not known.

Conclusions - Study #007US

This is a single-center study in which the original intent was to compare the results of the Crinone treatment group only to values drawn from historical data. Due to uncertainty regarding the historical values, this reviewer assessed the efficacy of Crinone by comparison only to a defined clinically meaningful value of zero for pregnancy rates among women with no endogenous production of progesterone who are undergoing a donor egg transfer procedure.

For the single center, the results indicate that, with 95% confidence, the population clinical pregnancy rate for the Crinone treatment at the Jones Institute for Reproductive Medicine (single center) is at least 34.8% and could be as high as 61.5%. This exceeds the value of zero, as do the 95% confidence intervals for the chemical and ongoing pregnancy rates for the Crinone treatment in this single center. The applicability of these results to the general population of women with no endogenous production of progesterone who are undergoing a donor egg transfer procedure is not known.

Two changes are suggested for the labeling regarding this study. The first is that the label should mention this is a single-center study. The other change reflects the true sample size in this study. The applicant listed a sample size of 50 subjects who received Crinone. This refers only to subjects included in the efficacy population from the original submission (11/96). A total of 64 subjects were randomized to the Crinone treatment, and 61 received the Crinone treatment, in the original submission. An additional 4 subjects were submitted as a safety update (2/97) for the Crinone treatment group, all of whom received treatment. All 68 subjects were combined for the analysis results presented here. The clinical pregnancy rate listed in the label (48%) remained the same, so the proposed change for the label is the sample size from 50 to 68.

STUDY # 1620-COL-F01

Background

Study # 1620-COL-F01 (F01) was a randomized, open-label, multicenter clinical trial with an active-control, oral progesterone (Utrogestan), as the comparator. The purpose of this study was to assess the efficacy and safety of Crinone in the luteal phase support of patients undergoing an in vitro fertilization (IVF) procedure. This study was conducted in Europe, where Utrogestan is approved for this indication. Only the Crinone treatment group was included for consideration with NDA 20-756 because Utrogestan is not approved for this indication in the U.S.

The sample consisted of women ages 22 to 41 years of age with tubal, idiopathic, or endometriosis-linked sterility, and normal ovulatory cycles, who had an embryo transfer as part of an IVF procedure. All subjects received a GnRH analogue for 21 days at least. This was the first to fourth IVF attempt for each subject.

Patients were randomly assigned, by a 1:1 ratio, to one of the 2 treatment groups at the time of embryo transfer, and treatment started within 24 hours after the embryo transfer procedure. On day 12 of treatment, a β-HCG pregnancy test was administered to determine chemical pregnancy, with the results known by the day 14 office visit. If the patient was not chemically pregnant, treatment was stopped on day 14. Otherwise treatment continued for a total of 30 days unless the pregnancy ended before that time.

The study originally planned to have 8 centers, all in Europe. At one center (#2) the investigator decided not to participate prior to beginning the study. Center #5, which had assigned 9 subjects to treatment (5 Crinone: 4 Utrogestan), was excluded from all analyses because the pharmacist gave subjects the wrong dosage of Crinone. One additional subject in the Utrogestan treatment group was excluded from analyses because the case report form was lost by the investigator.

Primary variables of interest are:

Variable	Time point
Chemical pregnancy rate (% transfer)	12 days after embryo transfer
Clinical pregnancy rate (% transfer)	30 days after embryo transfer
On-going pregnancy rate (% transfer)	90 days after embryo transfer
Delivery rate (% transfer)	completion of pregnancy

Secondary variable of interest is:

Variable	Time point
Number of newborns	completion of pregnancy

A total of 283 patients were randomized to the two treatment groups. The two groups were similar with regard to demographic characteristics at baseline, as shown in Table 7.

Table 7: Demographic characteristics (Study #F01)

	Crinone (n=139)		Utrogestan (n=144)	
Characteristic	Mean	S.D.	Mean	S.D.
Age (years)	31.8	3.3	31.6	4.0
Weight (lbs)	130.1	19.8	130.3	22.5
Height (inches)	64.4	2.2	64.4	2.3

Source: Vol.1.07, Appendix 9. (Scale transformations from SAS data sets)

The disposition of the subjects in the 2 treatment groups is shown in Tables 8 and 9. The reasons for discontinuation were not clearly documented. The study report provided only summaries of number of subjects at each visit. The distribution of the reasons and time points for discontinuations is similar for the 2 treatment groups.

Table 8: Disposition of subjects by group (Study #F01)

	Crinone		Utrogestan	
	n	rand. %	n	rand. %
Randomized	139	100.0	145	100.0
Have case report form	139	100.0	144	99.3
14-day visit	121	87.1	119	82.1
30-day visit	40 (1)	28.8	35	24.1
90-day visit	36	25.9	33 (2)	22.8
Delivered infant(s)	32	23.0	32	22.1

Source: Vol. 1.07, Section 3.

(1) Includes 2 subjects who discontinued treatment at the 14-day visit due to a negative chemical pregnancy test result but were later found to be pregnant.
(2) Includes 1 subject who discontinued treatment at the 14-day visit due to a negative chemical pregnancy test result but was later found to be pregnant.

Table 9: Reasons for Discontinuation (Study #F01)

	Crinone (n=139)		Utrogestan (n=145)	
	n	% rand.	n	% rand.
Did not return for 14-day visit *	18	12.9	25	17.2
Not chemically pregnant at 14-day visit (stopped trmt)	74	53.2	77	53.1
Not clinically pregnant at 30-day visit	9	6.5	7	4.8
No ongoing pregnancy at 90-day visit (early abortion)	4	2.9	3	2.1
No delivery (late abortion)	4	2.9	1	0.7

Source: Vol. 1.07, Section 3.

* Investigators assumed that if patient did not return for the 14-day visit, bleeding must have started, indicating the patient was not pregnant.

Applicant's Analysis

There were 10 subjects who were randomized to treatment but were not included in the efficacy analyses. Nine of these (5 Crinone; 4 Utrogestan) were from one center (#5) in which errors were made by the pharmacy in the dispensing on the study treatments (incorrect study product was dispensed to the Crinone patients). The other subject dropped did not have a CRF document. The medical officer agrees that these subjects should not be included in the efficacy analyses. The remaining 283 subjects are considered the intent-to-treat population for these analyses.

The applicant's analysis provided summaries by treatment group, shown in Table 10a, along with results of between group tests for treatment differences. The applicant performed Fisher's Exact and Chi-square tests for between group comparisons on the pregnancy and delivery rate variables and found no statistically significant treatment differences using alpha=.05 for each test. The intent was to show equivalence of Crinone to Utrogestan for the indication of support of the luteal phase after in vitro fertilization (IVF). The applicant's test results are not shown here because they are not appropriate for the equivalence hypotheses.

Based on the results of the between group comparisons, the applicant concluded that Crinone is effective in the luteal phase support after IVF procedures. All the subjects in this study received a GnRH analogue to suppress endogenous production of progesterone as part of the IVF procedure.

Table 10a: Applicant's Results (Intent-to-treat subjects): (Study #F01)

	Crinone		Utrogestan	
	n	% of DE Transfers	n	% of DE Transfers
Number of subjects	139	100.0	144	100.0
Primary Variables				
Chemical Pregnancy Rate	49	35.3	43	29.9
Clinical Pregnancy Rate	40	28.8	36	25.0
On-going Pregnancy Rate	36	25.9	33	22.9
Delivery Rate	32	23.0	32	22.2
Secondary Variable				
Number of Newborns	47	NA	48	NA

Source: Vol. 1.08, Section 4.1.

Reviewer's Analysis

The Fisher's Exact and Chi-square tests are not appropriate tests for the goal of demonstrating equivalence. Also, Utrogestan is not approved for this indication in the U.S. Therefore, in discussion with the medical officers, it was decided that the assessment of efficacy would rely on comparisons of confidence intervals to a clinically meaningful rate of zero for all efficacy variables. This is the same procedure as was used in this reviewer's analysis of the pivotal study, 007US.

The 95% confidence intervals for the Crinone treatment group are presented in Table 10b. All pregnancy rate variables exclude the value of zero. This supports the efficacy of Crinone for support of the luteal phase after in vitro fertilization (IVF).

Table 10b: Reviewer's Results (Intent-to-treat subjects): (Study #F01)

	Crinone			
	n	% of DE Transfers	Lower 95% Confidence Bound	Upper 95% Confidence Bound
Number of subjects	139	100.0		
Primary Variables				
Chemical Pregnancy Rate	49	35.3	27.3	43.2
Clinical Pregnancy Rate	40	28.8	21.3	36.3
On-going Pregnancy Rate	36	25.9	18.6	33.2
Delivery Rate	32	23.0	16.0	30.0
Secondary Variable				
Number of Newborns	47	NA	NA	NA

Subgroup Analyses

For descriptive purposes only, this reviewer compared the primary efficacy results for the Crinone treatment group by age group and center. Age group was split into 2 categories: 30 and Under, Over 30. There were no noteworthy differences or trends across either age or center for the efficacy variables.

Conclusions - Study #F01

Study F01 is a clinical trial in which Crinone was administered to women undergoing an IVF procedure. As part of the IVF procedure, the women received a GnRH analogue to suppress endogenous progesterone production. The results of the Crinone treatment group were compared only to a clinically meaningful rate of zero for the pregnancy variables. The 95% confidence intervals for all pregnancy rate variables exclude zero. This supports the efficacy of Crinone in support of the luteal phase of pregnancy in women with suppressed endogenous progesterone during an IVF procedure. With 95% confidence, the population clinical pregnancy rate among women randomized to the Crinone treatment is at least 21.3% and could be as high as 36.3%.

Summary (Studies 007US & F01)

The goal of these studies was to show that Crinone is effective for initiating and maintaining pregnancy in women undergoing ART procedures. Both studies included an active-control comparator which was not approved for this indication in the U.S. The decision of the medical officers was to compare Crinone only to a clinically meaningful value, not to make comparisons with the active-control treatment groups. Clinically meaningful values proposed by the applicant based on historical experience were not well documented, raising concerns about the appropriateness of their use for comparisons.

Discussions with the Medical Officers concluded that, for women with no endogenous (or medically suppressed) production of progesterone, the pregnancy rate would be zero without progesterone supplementation. Therefore, it was decided that a reasonable assessment of the efficacy for the Crinone treatment would be confidence intervals on the observed pregnancy rates for the Crinone treatment group only. The efficacy analysis consisted of comparing the 95% confidence intervals for each of the primary variables (pregnancy rates) to the clinically meaningful value of zero. Confidence intervals which exclude zero support the efficacy of Crinone. In both studies, the 95% confidence intervals for all the pregnancy rates excluded zero.

Study 007US was a single-center study. The suitability of generalizing the results from this study to the entire population of women with no endogenous production of progesterone who are undergoing a donor egg transfer procedure at all centers is not known.

The following are changes suggested for the proposed label:

Katherine B Meaker

Katherine B Meaker, M.S.
Mathematical Statistician

Concur: Dr. Nevius

Dr. Kammerman 5/8/97

cc:
Archival NDA 20-756
HFD-580
HFD-580/RBennett, HJolson, LRarick
HFD-580/DMoore
HFD-715/ENevius, LKammerman, KMeaker, Chron

KBM/7-May-97/Word 7.0\My Documents\NDA20756-Crinone\Review