

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-057

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 22-057

Drug Name: Endometrin (progesterone effervescent vaginal tablet, 100 mg)

Indication(s): Pregnancy Through Progesterone Supplementation as Part of an (ART) Treatment Program. T † **b(4)**

Applicant: Ferring Pharmaceuticals Inc.

Date(s):

Submission: August 21, 2006

User Fee Goal: June 21, 2007

Review Priority: Standard

Biometrics Division: Division of Biometrics 3

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Keywords:

NDA Review, Clinical Study, Open-Label, Assessor-Blind, Step-Down Procedure, Non-Inferiority

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES	3
1.3 STATISTICAL ISSUES AND FINDINGS	3
2. INTRODUCTION.....	4
2.1 OVERVIEW.....	4
2.2 DATA SOURCES	4
3. STATISTICAL EVALUATION	4
3.1 EVALUATION OF EFFICACY	5
3.2 EVALUATION OF SAFETY.....	8
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	9
4.1 GENDER, RACE AND AGE	9
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	9
5. SUMMARY AND CONCLUSIONS	9
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	9
5.2 CONCLUSIONS AND RECOMMENDATIONS	10

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant has submitted data from a randomized, open-label clinical trial (Study # 2004-02) to support the efficacy of Endometrin in the treatment of infertile women undergoing assisted reproductive technology (ART). The objective of the trial was to demonstrate that the pregnancy rates treated with Endometrin doses (100 mg BID or 100 mg TID) were non-inferior to pregnancy rate treated with Crinone 8% QD, an active comparator. Based on the sponsor's data and confirmed by our analysis, pregnancy rate in Endometrin 100 mg TID treated subjects was statistically non-inferior to Crinone and pregnancy rate in Endometrin 100 mg BID was marginally non-inferior to Crinone.

1.2 Brief Overview of Clinical Study

Study 2004-02 was a 10-week, multicenter, randomized, open-label, assessor-blinded study of a vaginal micronized progesterone tablet in healthy female pre-menopausal subjects between 18 and 42 years of age undergoing In Vitro Fertilization (IVF). A total of 1211 subjects were analyzed in this study: 404 subjects in the Endometrine 100 mg BID, 404 in 100 mg TID and 403 in the Crinone treatment arm.

The study objective was to determine that the efficacy of Endometrin is non-inferior to Crinone. The primary efficacy endpoint (ongoing pregnancy rate) was defined as identification of fetal heart movement at approximately 6 weeks of gestation, following one IVF treatment cycle.

To declare non-inferiority, the lower bound of a 95% CI for the differences in the pregnancy rates between each Endometrin arm vs. Crinone was to exclude a difference greater than 10%.

1.3 Statistical Issues and Findings

This was an open-label, assessor-blind study. The lack of double-blinding may have introduced bias in the study conduct. Therefore, the results of the study should be interpreted with caution.

In addition, the distributions of "the number of embryos transferred" did not come from a normal distribution and are not similar among the three treatment groups. For that reason a non-parametric method was used to compare these means. Using a Wilcoxon method the p value was still significant (p=0.043). Therefore, another possible bias might exist in the analyses of this primary endpoint variable. This causes, yet, another concern in interpretation of the results of this study.

Using a step-down procedure for multiple comparison, pregnancy rates in Endometrin 100 mg TID was found to be statistically non-inferior to Crinone 8% QD, with the lower bound of the 95% CI of -6.7%. However, the Endometrin 100 mg BID arm showed a borderline non-inferiority with a lower bound of -10.3%.

<u>Treatment Arm</u>	<u>Pregnancy Rates</u>	<u>Differences vs. Crinone</u>	<u>CI (95%)</u>
Endometrin 100 mg BID	156/404=38.6%	-3.6%	(-10.3%, 3.2 %)
Endometrin 100 mg TID	171/404=42.3%	+0.1%	(-6.7%, 6.9%)
Crinone	170/403=42.2%	--	--

2. INTRODUCTION

Ferring Pharmaceuticals Incorporated has developed a vaginal progesterone supplementation tablet for the treatment of infertile women undergoing Assisted Reproductive Technology (ART). It is typically administered, vaginally, two or three times a day (BID or TID) using an applicator.

2.1 Overview

The application consists of one study (Study 2004-02). This study was a Phase 3, 10-week, multicenter (25 US investigators), randomized, open-label, assessor-blinded of a vaginal micronized progesterone tablet in healthy female pre-menopausal subjects between 18 and 42 years of age undergoing In Vitro Fertilization (IVF). Subjects were randomized to 1 of 3 treatment groups in a ratio of 1:1:1 on the day or the day after oocyte retrieval. A total of 1211 subjects participated in the study; 404 subjects in the Endometrine 100 mg BID, 404 in 100 mg TID and 403 in the Crinone 8% QD treatment arm. The study drug was initiated on the day after oocyte retrieval. Each subject who became pregnant continued with the study drug for a total duration of 10 weeks.

The study objective was to determine the efficacy of Endometrin administered vaginally in terms of ongoing pregnancy rates in women undergoing IVF. The primary efficacy endpoint (ongoing pregnancy rate) was defined as identification of fetal heart movement at approximately 6 weeks of gestation, following one IVF treatment cycle.

This was an open-label, assessor-blind study. The sponsor argued that since the tablet and the gel formulation of the two products are different, therefore, the double-blinding would not be possible. For that reason, the study was assessor-blinded. In other words, the person who performed the trans-vaginal ultrasound (TVU) to confirm clinical and ongoing pregnancy was blinded to the subject's treatment assignment. However, the lack of double-blinding of the study causes concerns since it might introduce bias in the conduct of the study. Therefore, the results of the study should be interpreted with caution.

2.2 Data Sources

The Sponsor has provided the study report and the SAS data electronically. The electronic data is located: \\Cdsesub1\n22057\N_000\2006-08-21\m5

3. STATISTICAL EVALUATION

The primary statistical analysis was performed to determine whether the ongoing pregnancy rate for each dose of Endometrin was non-inferior to Crinone. This was accomplished by first calculating the pregnancy rate in each treatment arm and ultimately calculating a 95% CI for the differences in the pregnancy rates between each Endometrin arm vs. Crinone. To declare non-inferiority, the lower bound of the confidence interval was to exclude a difference greater than 10%. To adjust for multiple comparisons, a step-down procedure was used such that Endometrin 100 mg TID versus Crinone was considered the primary comparison.

A sample size of at least 990 subjects with no less than 330 per group was planned. This sample size was calculated based on 80% power, an estimated Crinone pregnancy rate of 30% using a two-sided 95% confidence interval and a pre-specified non-inferiority margin of 10% to demonstrate the non-inferiority of Endometrin vs. Crinone in the pregnancy rate.

A total of 1211 subjects were randomized into the study. Of which, 404 subjects participated in the Endometrin 100 mg BID, 404 in 100 mg TID and 403 in the Crinone 8% QD treatment arm. Intent-to-Treat (ITT) population was “subjects who were randomized to a study drug and took at least 1 dose of the study drug.” This review focuses, only, on the ITT population.

3.1 Evaluation of Efficacy

Of the 1211 subjects randomized to the study, 465 (38%) completed the 10 weeks of treatment, 710 (59%) discontinued the study and 36 (3%) did not undergo embryo transfer. No statistically significant differences were observed between each Endometrin group and the Crinone arm in the rate of subjects who failed to complete the study. The most common reason for discontinuation was “no positive pregnancy test at visits 3 or 4” (548/710=77%).

The Demographic and Baseline Characteristics: The demographics and baseline characteristics of the subjects in the three treatment arms were compatible with each other. No statistically significant differences were observed among the treatment arms in regards to the demographics and baseline characteristics of the subjects. Age range was 19 to 42 years with a mean of 33 years in all 3 arms. Approximately, 39% of the subjects were 35 years or older. The majority of the subjects were Caucasian (74%).

The subject’s weight ranged from 88 to 235 pounds and height ranged from 49 to 73 inches. The majority of the subjects in each treatment arm had a BMI ranging from 18.5 and 24.9 kg/m², with a mean of approximately 25 kg/m² in each group. Table 1 shows the distribution of the subjects based on their BMI category by treatment arm.

Table 1: Distribution of the Subjects Based on their BMI Category

Treatment Group	BMI				Total
	<20	=20 to <25	=25 to <30	=>30	
Endometrin 100 mg BID	33 (8%)	182 (45%)	121 (30%)	66 (16%)	402 (33%)
Endometrin 100 mg TID	35 (9%)	174 (43%)	120 (30%)	75 (19%)	404 (33%)
Crinone 8% QD	34 (8%)	190 (47%)	112 (28%)	66 (16%)	402 (33%)
Total	102	546	353	207	1208

Infertility diagnoses were similar across the 3 treatment groups. The subjects, in all the treatment groups, had been pregnant between 0 and 12 times, with full-term births ranging from one to 7. The median duration of treatment among “completers” was 67 days and among subjects who did not complete the study was 13 days for all the treatments arms.

Number of Embryos Transferred: A total of 1175 (97%) of the subjects had embryos transferred. Table 2 shows the number of embryos transferred by treatment group.

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Table 2: The Number of Embryos Transferred

Treatment Group	# of Embryos Transferred							
	1	2	3	4	5	6	7	Total
100 mg BID	16 (4%)	211 (54%)	159 (41%)	4 (1%)	1 (0.3%)	1 (0.3%)	0 (0%)	392 (33%)
100 mg TID	15 (4%)	211 (54%)	160 (41%)	1 (0.3%)	2 (0.5%)	0 (0%)	1(0.3%)	390 (33%)
Crinone 8% QD	31 (8%)	220 (56%)	137 (35%)	4 (1%)	1 (0.3%)	0 (0%)	0 (0%)	393 (33%)
Total	62	642	456	9	4	1	1	1175

Although the mean and the standard deviation for the number of embryos transferred were similar in all the treatment groups, however, statistically significant differences were observed when each Endometrin dosage was compared to Crinone treatment arm. The means for the number of embryos transferred along with the associated p values are presented in Table 3.

Table 3: Mean Number of Embryos Transferred

	Endometrin 100 mg BID (n=404)	Endometrin 100 mg TID (n=404)	Crinone 8% QD (n=403)
# of Embryos Transferred	392	390	393
Mean (SD)	2.4 (0.62)	2.4 (0.64)	2.3 (0.64)

The distributions for “the number of embryos transferred” do not come from a normal distribution and are not similar among the three treatment groups. For that reason a non-parametric method was used to compare these means. Using a Wilcoxon method the p value was still significant (p=0.043). Therefore, another possible bias might exist in the analyses of this primary endpoint variable. This causes, yet, another concern in interpretation of the results of this study.

Analysis of the Primary Efficacy Endpoint: The primary efficacy variable was ongoing pregnancy, defined as identification of fetal heat movement at approximately 6 weeks of gestation.

A total of 404 subjects had been treated with Endometrin 100 mg BID. Of which 156 (38.6%) had ongoing pregnancy with a 95% CI of (33.8%, 43.6%). Also, 404 subjects received Endometrin 100 mg TID, which 171 (42.3%) with a 95% CI of (37.5%, 47.3%). A total of 403 subjects were treated with Crinone 8% gel QD; 170 (42.2%) and a 95% CI of (37.3%, 47.2%).

Difference in rates between Endometrin BID & Crinone was -3.8% (95% CI: -10.3%, 3.06%) and for Endometrin TID & Crinone was +0.1% (95% CI: -6.7%, 6.9%)

Tables 4 and 5, respectively, show the sponsor’s and the reviewer’s presentation of the pregnancy rates based on fetal heart rate for all the treatments arms. Note that the Sponsor has used the per-protocol population in their analysis of efficacy while in this review, the ITT population was used. Therefore, the results might be somewhat different.

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Table 4: Sponsor's Pregnancy Rate based on Fetal Heart Movement

Ongoing Pregnancy	Endometrin 100 mg BID	Endometrin 100 mg TID	Crinone 8% gel QD
Efficacy Population	(N=392)	(N=390)	(N=393)
Pregnancy Rate	156 (40%)	171 (44%)	170 (43%)
95% Confidence Interval (CI)	[34.9, 44.8]	[38.9, 48.9]	[38.3, 48.3]
Difference between Endometrin & Crinone [95% CI lower bound for difference]	-3.5% [-10.4]	0.6% [-6.4]	
ITT Population	(N=404)	(N=404)	(N=403)
Pregnancy Rate	156 (39%)	171 (42%)	170 (42%)
95% Confidence Interval	[33.8, 43.6]	[37.5, 47.3]	[37.3, 47.2]
Difference between Endometrin & Crinone [95% CI lower bound for difference]	-3.6% [-10.3]	0.1% [-6.7]	
Per-Protocol Population	(N=377)	(N=377)	(N=375)
Pregnancy Rate	149 (40%)	166 (44%)	161 (43%)
95% Confidence Interval	[34.6, 44.7]	[39.0, 49.2]	[37.9, 48.1]
Difference between Endometrin & Crinone [95% CI lower bound for difference]	-3.4% [-10.4]	1.1% [-6.0]	
Completers Population	(N=147) ^a	(N=158) ^a	(N=160) ^a
Pregnancy Rate	147 (100%)	158 (100%)	160 (100%)
95% Confidence Interval	[97.5, 100.0]	[97.7, 100]	[97.7, 100]
Difference between Endometrin & Crinone [95% CI lower bound for difference]	0.0% [not applicable]	0.0% [not applicable]	

Table 5: Reviewer's Pregnancy Rate Based on Presence of Fetal Heart Rate– ITT Population

Ongoing Pregnancy	Endometrin 100 mg BID N=404	Endometrin 100 mg TID N=404	Crinone 8% gel QD N=403
Pregnancy Rate (95% Confidence Interval)	156/404=38.6% (33.8%, 43.6%)	171/404=42.3% (37.5%, 47.3%)	170/403=42.2% (37.3%, 47.2%)
Difference in Rates Between Endometrin & Crinone (95% Confidence Interval)	-3.6% (-10.3%, 3.2 %)	+0.1% (-6.7%, 6.9 %)	--

Analysis of the Primary Efficacy Endpoint by Age Category: A total of 336 (46%) of the subjects who were younger than 35 years old got pregnant, vs. 161 (34%) of the women 35 and older who had ongoing pregnancy. In general, younger women (less than 35 years of age) did better in terms of the ongoing pregnancy than their older counter parts.

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Table 6: Reviewer’s Pregnancy Rate by Two Age Categories: 35 and Older/ Younger than 35 years ITT Population

Age Category		Endometrin 100 mg BID N=404	Endometrin 100 mg TID N=404	Crinone 8% gel QD N=403
Younger than 35	Ongoing Pregnancy Rate 95% CI for the Rate	111/247=44.94% (38.63%, 51.37%)	117/247=47.37% (41.00%, 53.80%)	108/243=44.44% (38.09%, 50.93%)
	Difference with Crinone 95% CI for the Difference	0.50% (-8.37%, 9.36%)	2.93% (-5.92%, 11.76%)	
35 and Older	Ongoing Pregnancy Rate 95% CI for the Rate	45/157=28.66% (21.74%, 36.41%)	54/157=34.39% (27.01%, 42.39%)	62/160=38.75% (31.16%, 46.76%)
	Difference with Crinone 95% CI for the Difference	-10.09% (-20.3, 0.3%)	-4.36% (-14.9, 6.3%)	

Both Endometrin BID and TID appear to be comparable to Crinone treatment arm in regards to the ongoing pregnancy rate. For the age group of younger than 35, the difference in pregnancy rates between Endometrin BID vs. Crinone was 0.5% with a 95% CI of (-8.37%, 9.36%); and between Endometrin TID vs. Crinone was 2.93% and a 95% CI of (-5.92%, 11.76%).

Analysis of the Primary Efficacy Endpoint by BMI: In order to determine whether there were any differences between subjects with higher BMI vs. lower BMI, in this review, the subjects were categorized in four different BMI groups, as follows:
BMI<20, BMI=20 to <25, BMI=25 to <30 and BMI=>30.

In general (ignoring the treatment group), the lighter subjects did better than the heavier groups. In total 49 out of 102 (48%) of the subjects in the BMI<20, 236 out of 546 (43%) subjects in the BMI=20 to <25, 140 out of 353 (40%) of the BMI=25 to <30 group and only 72 of 207 (35%) of the heaviest group (BMI=>30) had ongoing pregnancies. The difference among these proportions were not statistically significant (p=0.08).

When the analyses of efficacy (the rate on ongoing pregnancy by treatment arm) were repeated, this time controlling for obesity, the results were not statistically significant (p=0.3).

Number of Embryos Transferred: A total of 1175 (97%) of the subjects had embryos transferred. Table 2 which was shown previously in this review, illustrates the number of embryos transferred by treatment group.

The distributions of “the number of embryos transferred” were not similar among the treatment groups. In other words, it seemed that a higher number of embryos were transferred in the Endometrin TID arm. However, when the analyses were repeated, controlling for the number of embryos transferred, the results did not change.

3.2 Evaluation of Safety

This review focuses, solely, on the evaluation of efficacy.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Because of the nature of this drug's indication, the study was done, exclusively, on females. The majority of them (74%) were Caucasian. Therefore, no subgroup analyses were deemed necessary for gender and race. However, analyses were done for two different age categories of the subjects; younger than 35 years of age and 35 years and older.

In general, younger women (less than 35 years of age) did better in terms of the ongoing pregnancy than their older (35 and older) counterparts. Not considering treatment arm, in total, 336 out of 737 (45.6%) of younger subjects and 161 of the 474 (34%) in older group had ongoing pregnancies.

For the age group of younger than 35, both Endometrin BID and TID appear to be comparable to Crinone treatment arm in regards to the ongoing pregnancy rate. The difference in pregnancy rates between Endometrin BID vs. Crinone was 0.5% with a 95% CI of (-8.37%, 9.36%); and between Endometrin TID vs. Crinone was 2.93% and a 95% CI of (-5.92%, 11.76%).

4.2 Other Special/Subgroup Populations

Analyses were done for BMI of the subjects. In order to determine whether there were any differences between subjects with higher BMI vs. lower BMI, in this review, the subjects were categorized in four different BMI groups in the following manner:
BMI<20, BMI=20 to <25, BMI=25 to <30 and BMI=>30.

In general (ignoring the treatment group), the lighter subjects did better in general than the heavier groups. In total 49 out of 102 (48%) of the subjects in the BMI<20, 236 out of 546 (43%) subjects in the BMI =20 to <25, 140 out of 353 (40%) of the BMI=25 to <30 group and only 72 of 207 (35%) of the heaviest group (BMI=>30) had ongoing pregnancies. The difference among these proportions were not statistically significant (p=0.08).

When the analyses of efficacy (the rate on ongoing pregnancy by treatment arm) were repeated, this time controlling for obesity, the results were not statistically significant (p=0.3).

5. SUMMARY AND CONCLUSIONS

Using a step-down procedure for multiple comparison, pregnancy rates in Endometrin 100 mg TID was found to be statistically non-inferior to Crinone 8% QD, with the lower bound of the 95% CI of -6.7%. However, the Endometrin 100 mg BID arm showed a borderline non-inferiority with a lower bound of -10.3%.

<u>Treatment Arm</u>	<u>Pregnancy Rates</u>	<u>Differences vs. Crinone</u>	<u>95% CI</u>
Endometrin 100 mg BID	156/404=38.6%	-3.6%	(-10.3%, 3.2 %)
Endometrin 100 mg TID	171/404=42.3%	+0.1%	(-6.7%, 6.9 %)
Crinone	170/403=42.2%		

5.1 Statistical Issues and Collective Evidence

Lack of double-blinding may have introduced bias in this open-label, assessor-blind study. Therefore, the results of the study should be interpreted with caution. In addition, the distributions of "the number of

embryos transferred" were not similar among the treatment groups. In other words, it seemed that a higher number of embryos were transferred in the Endometrin TID arm. Therefore, another possible bias might exist in the analyses of this primary endpoint variable. This causes, yet, another concern in interpretation of the results of this study.

5.2 Conclusions and Recommendations

Pregnancy rates in Endometrin 100 mg TID was found to be statistically non-inferior to Crinone 8% QD, with the lower bound of the 95% CI of -6.7%. However, the Endometrin 100 mg BID arm showed a borderline non-inferiority with a lower bound of -10.3%.

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Shahla Farr
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Mahboob Sobhan
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STATISTICAL EVALUATION OF NEW NDAs - FILEABILITY

NDA: 22-057
Drug Name: Endometrin
Sponsor: Ferring Pharmaceuticals.
Indications: Progesterone for assisted reproductive technology
Medical Officer: Audrey Gassman, M.D., HFD-580
Statistician: Mahboob Sobhan, Ph.D., HFD-715
Project Manager: John Kim
Submission Date: 8/21/2006
45 day Meeting Date: 10/3/2006

Summary of Studies

This submission included efficacy data from one randomized, open-label, placebo-controlled study (Protocol #2004-02) to support the above indication. The following items were checked to determine the fileability of the submission.

Items:	Check (Yes, No, N/A)	Comments:
Index sufficient to locate reports, tables, etc.	Yes	
Original protocols and subsequent amendments included in the submission.	Yes	
Designs utilized appropriate for the indications requested.	Yes	
Endpoints and methods of analyses spelled out in the protocols.	Yes	
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	No	Not planned
Appropriate references included for novel statistical methodology (if present)	yes	
Sufficient data listings and intermediate analysis tables to permit a statistical review	Yes	
Data from primary studies on diskettes and/or eCTD submitted	yes	Data submitted in the EDR
Effects of dropouts on primary analyses investigated.	yes	
Integrated summary of safety and efficacy included.	Yes	Safety only.

Conclusion

After the preliminary review of the submission, we have not identified any deficiencies that would be a reason for refuse-to-file. The sponsor provided the required information in this NDA to perform statistical evaluation and therefore, this NDA is fileable.

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