CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21047

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

NDA No: 21-047 Date: AUG 4 1999

Applicant: Ferring Pharmaceuticals Inc.

Name of Drug: Repronex™ (menotropins for injection) 75/150 IU Vial

Indications: 1. Induction of follicle development for in-vitro fertilization
2. Induction of follicle development for ovulation in anovulatory and oligoovulatatory infertile female patients

Project Manager: Diane Moore (HFD-580)

Medical Reviewer: Dr. Ridgley Bennett (HFD-580)

Statistical Reviewer: Moh-Jee Ng, M.S. (HFD-715)

Documents Reviewed: Vol. 1.2, 1.4, 1.10, 1.10A-1.10B, 1.11, 1.11A-1.11D

User Fee Due Date: August 14, 1999 (10 months)

Introduction

Repronex™ has been approved by FDA under an ANDA as equivalent to Pergonal for induction of ovarian follicles for ovulation induction and for In-vitro Fertilization (IVF) in women, and for spermatogenesis in men. Human Chorionic Gonadotropin (hCG), a naturally occurring hormone in post-menopausal urine, is detected in Repronex™. Ovulation and spermatogenesis require an additional administration of hCG. In this NDA, the applicant has submitted the results of 2 clinical trials, one to support the indication of induction of follicle development for in-vitro fertilization, and the other to support the indication of induction of follicle development for ovulation in anovulatory and oligoovulatory infertile female patients. Repronex™ is administered by intramuscular (IM) or subcutaneous (SC) injection. The objectives are to determine the therapeutic efficacy and safety of Repronex intramuscular and Repronex subcutaneous in comparison to Pergonal I.M.

These two studies were conducted in the US. FPI Rep 97-02 evaluated female patients undergoing IVF and FPI Rep 97-01 evaluated oligoovulatory infertile female patients. Both studies had randomized, parallel group, multicenter designs comparing Repronex™ IM, Repronex™ SC and Pergonal® IM. Table 1 summarizes these two studies.

Table 1

Summary of Open-label, Parallel Group, Randomized Clinical Studies

Study Number Start/Completed Date	Type of Study	Treatment Arms (# Randomized)	Indication	Duration of Treatment
FPI Rep 97-01 1/98 – 1/99	A randomized, open-label, Parallel group, multicenter	Repronex IM (N=36) Repronex SC (N=36) Pergonal IM (N=36)	Induction of follicle development for ovulation in anovulatory and oligoovulatory infertile Female patients	Up to 12 days
FPI Rep 97-02 12/97 – 6/98	A randomized, open-label, Parallel group, multicenter	Repronex IM (N=65) Repronex SC (N=60) Pergonal IM (N=61)	Induction of follicle development for in-vitro fertilization	Up to 12 days

Study FPI Rep 97-02

FPI Rep 97-02 is a randomized, open-label, parallel group, multicenter, efficacy study comparing one cycle of treatment with Repronex S.C., Repronex I.M., and Pergonal I.M. at doses of 150 IU to 450 IU/day in female patients undergoing in-vitro fertilization. Treatment was up to 12 days until the presence of at least 3 follicles, each greater than or equal to 16 mm in size. Ten thousand (10,000 USP units I.M.) of hCG were then administered to induce ovulation.

The primary efficacy variable was:

Number of oocytes retrieved per cycle

Secondary efficacy variables were:

Percentage of cycles with oocytes retrieval
Peak serum E_2 levels
Percentage of cycles with embryo transfer
Percentage of cycles with chemical pregnancies
Percentage of cycles with clinical pregnancies
Percentage of cycles with continued pregnancies

Patient Disposition

A total of 189 patients enrolled and 186 were accepted to receive gonadotropins. Each of the 186 patients was randomly assigned to one of the three treatment groups. The patient disposition by treatment group is shown in Table 2.

Table 2
Study FPI Rep 97-02 Patient Disposition

Treatment Group N (%)	Intent-to-treat population N=186		
	Repronex I.M.	Repronex S.C.	Pergonal I.M.
Intent-to-treat	65 (100%)	60 (100%)	61 (100%)
Did not receive hCG*	4 (6%)	5 (8%)	5 (8%)
Primary efficacy responder**	61 (94%)	55 (92%)	56 (92%)

* Did not receive hCG due to inadequate response, adverse event, risk of OHSS, protocol violation, patient choice, or other specified reason.

** The primary efficacy responders who received hCG and for whom number of ooctyes retrieved could be measured.

Demographics

Treatment groups were comparable with regard to demographic and infertility characteristics. The mean age of the patients was 32 years. The patients were between 20 and 39 years. There was no statistically significant ($p<0.05$) differences among the three treatment groups in any of the baseline demographic parameters. Prior infertility history was obtained in terms of duration, number of full and pre-term births, number of abortions/miscarriages, number of ectopic pregnancies, number of living children, number with previous IVF/GIFT/PROST cycles and number with previous cycles excluding IVF using gonadotropin therapy.

Sponsor's Efficacy Results

The sponsor analyzed both the intent-to-treat population and the subgroup of the primary efficacy responders. The intent-to-treat population included all patients who were randomized; the primary efficacy responders comprised those patients who receive hCG and underwent ooctyes retrieval. The sponsor compared the treatment groups using one-way ANOVA and Student's t-tests.

The analysis of the primary efficacy variable, number of oocytes retrieved per patient, showed no statistically significant differences for either the intent-to-treat or primary efficacy responder (received hCG) populations.

The analysis of the secondary efficacy variables included percentages of cycles of chemical, clinical and continuing pregnancy. There was a statistically significant difference between the patients with continuing pregnancies for Repronex S.C. compared with Pergonal I.M.

The sponsor concluded that Repronex™ I.M. and S.C. were equal in effectiveness, safety and tolerance to Pergonal® I.M. in ovarian stimulation for IVF. Repronex S.C. showed numerically better results for chemical and clinical pregnancies and statistically superior results for continuing pregnancy compared with Pergonal I.M. in the primary efficacy responder analysis.

Reviewer's Efficacy Results

The sponsor claimed equal effectiveness between Repronex I.M. and Pergonal I.M., and between Repronex S.C. and Pergonal I.M. These claims are based on the lack of statistical significance between the investigational products and the active control. However, lack of statistical significance does not necessarily imply "therapeutic equivalence". Therefore this reviewer's analysis computes 95% confidence intervals (adjusted for multiple comparisons) in order to help assess whether clinically important differences have been excluded.

Tables 4 and 5 present this reviewer's analysis of primary and secondary efficacy results for the intent-to-treat and primary responders group. The therapeutic efficacy of Repronex I.M. and Repronex S.C. compare to Pergonal I.M. on 1 cycle using the One-way ANOVA. Ninety-five percent confidence intervals for differences between treatments were calculated. These confidence intervals were adjusted for multiple comparisons by the Sidak method.

Table 4
Reviewer's Primary Efficacy Result for Study FPI Rep 97-02

	Mean (SD)			Adjusted P value		
	Repronex I.M.	Repronex S.C.	Pergonal I.M.	Diff (P –RI) • 95% CI on diff	Diff (P –RS) • 95% CI on diff	Diff (RI –RS) • 95% CI on diff
Intent-to-Treat						
	N=65	N=60	N=61			
Total oocytes retrieved	13.6(±7.7)	12.7(±7.8)	13.6(±7.8)	1.0 .0* (-3.3,3.4)	.0.87 0.9* (-2.4,4.4)	.0.88 .9** (-2.4,4.3)
Mature oocytes retrieved	9.4(±6.1)	8.6(±6.8)	9.3(±6.1)	1.0 -0.1* (-2.9,2.6)	.92 .7* (-2.1,3.4)	.86 .8** (-2.,3.5)
Primary Responders (Received hCG)						
	N=61	N=55	N=56			
Total oocytes retrieved	14.5(±7.1)	13.8(±7.1)	14.9(±6.9)	.99 .4* (-2.8,3.5)	.83 1.1* (-2.2,4.2)	.94 .7** (-2.5,3.8)
Mature oocytes retrieved	10.0(±5.7)	9.4(±6.6)	10.1(±5.8)	1.0 .1* (-2.6,2.8)	.90 .7* (-2.,3.5)	.92 .6** (-2.1,3.3)

• P=Pergonal I.M. , RI= Repronex I.M., RS=Repronex S.C.
* A positive difference favors Pergonal I.M.
** A positive difference favors Repronex I.M.

Table 5
Review's Secondary Efficacy Results of Study FPI Rep 97-02

	N (%)			Adjusted P value		
	Repronex I.M.	Repronex S.C.	Pergonal I.M.	Diff (P-RI) • 95% CI on diff	Diff (P-RS) • 95% CI on diff	Diff (RI-RS) • 95% CI on diff
Intent-to-Treat						
	N=65	N=60	N=61			
Pts w/Embryo transfer	58 (89.2)	51 (85)	55 (90.2)	.99 .01* (-.4,.6)	.59 .05* (-.3,.8)	.76 .04** (-.4,.8)
Pts w/chemical pregnancy	31 (47.7)	35(58.3)	32 (52.5)	.93 .05* (-.2,.3)	.89 -.06* (-.3,.2)	.56 -.1** (-.3,.1)
Pts w/clinical pregnancy	25 (38.5)	30 (50)	24 (39.3)	1.0 .01* (-.2,.2)	.56 -.1* (-.3,.1)	.48 -.1** (-.3,.1)
Pts w/continuing pregnancy	24 (36.9)	29 (48.3)	19 (31.1)	.88 -.06* (-.3,.2)	.15 -.2* (-.4,.04)	.47 -.1** (-.3,.1)
Primary Responders (Received hCG)						
	N=61	N=55	N=56			
Pts w/Embryo transfer	58 (95.1)	51 (92.7)	55 (98.2)	.85 .03* (-.3,.6)	.37 .06* (-.2,.8)	.82 .02** (-.3,.6)
Pts w/chemical pregnancy	31 (50.8)	35(63.6)	32 (57.1)	.87 .06* (-.2,.3)	.87 -.06* (-.3,.2)	.42 -.1** (-.4,.1)
Pts w/clinical pregnancy	25 (41)	30 (54.6)	24 (42.9)	1.0 .02* (-.2,.3)	.52 -.1* (-.3,.1)	.38 -.1** (-.4,.09)
Pts w/continuing pregnancy	24 (39.3)	29(52.7)	19(33.9)	.91 -.05* (-.3,.2)	.13 -.2* (-.4,.04)	.37 -.1** (-.4,.09)

• P=Pergonal I.M., RI= Repronex I.M., RS=Repronex S.C.
* A positive difference favors Pergonal I.M.
** A positive difference favors Repronex I.M.

This reviewer's results agreed with the sponsor's results that there are no statistically significant differences in the primary efficacy variables for both the intent-to-treat and primary responder groups. However, there is no statistically significant difference between the patients with continuing pregnancies for Repronex S.C. compared with Pergonal I.M for the primary responder group after adjustment for multiple comparisons.

The confidence intervals in Tables 4 and 5 must be examined by the medical reviewer to determine their clinical significance.

In this study a total of 39 patients had multiple pregnancies (see below Table 6); these differences were not statistically significant. However, the observed rates are greater for Repronex S.C. than for Repronex I.M. or Pergonal I.M.

Table 6
Multiple Pregnancies – primary responders

	Repronex I.M. N=10	Repronex S.C. N=15	Pergonal I.M. N=14
Twins	7 (70)	9 (60)	10 (71.4)
Triplets	3 (30)	3 (20)	3 (21.4)
Quadruplets	0 (0)	3 (20)	1 (7.1)

Source: Vol 8A of 15, Table 6A, page 42

Study FPI Rep 97-01

Study FPI Rep 97-01 is a randomized, open-label, parallel group, multicenter study comparing one cycle of treatment with Repronex S.C., Repronex I.M., or Pergonal I.M. at doses of 150 to 450 IU/day for up to 12 days in anovulatory or oligoovulatory infertile female patients for ovulation induction. One hundred and fourteen patients were enrolled and were randomly assigned to one of the three treatment groups.

Primary efficacy variable was:

Percentage of patients with ovulation

Secondary efficacy variables were:

Percentage of cycles with follicle development meeting hCG criteria
Number of follicles recruited per cycle meeting hCG criteria
Peak serum E_2 level

Demographics

There were no statistically significant differences between treatment groups with respect to any of the demographic or baseline characteristics.

Disposition of Subjects

One hundred and fifteen patients were enrolled in the study. One hundred and eight were accepted to receive gonadotropin therapy and were randomized into one of the three treatment groups. The Table 7 below summarizes patient disposition and reasons for early discontinuation by treatment group.

Table 7
Study FPI Rep 97-01 Patient Disposition

Parameter	Repronex I.M.	Repronex S.C.	Pergonal I.M.
Randomized	36	36	36
Completed Study	25	27	21
Did Not Complete Study	11	9	15
	Reasons for Discontinuation		
Failure to down regulate	0	0	0
Non-compliance	0	0	0
Decline in E_2 levels	0	0	4
Inadequate response	10	7	7
Protocol Violation	0	0	1
Risk of OHSS	0	1	3
Elevated E_2 levels/too many follicles	1	0	0
Lost to follow-up	0	1	0

Source: Vol 8H1 of 24, Table 3, page 34

Sponsor's Efficacy Results

This study compared the therapeutic effects of Repronex I.M., Repronex S.C., and Pergonal I.M. for ovulation induction in oligoovulatory patients. The sponsor performed analyses on an intent-to-treat group with all patients who were randomized and had cycles initiated with exogenous gonadotropins, and for the subsets of patients who received hCG and who ovulated. The sponsor compared the treatment groups using chi-squared tests.

The primary efficacy variable was ovulation. The sponsor concluded there were no significantly differences among the treatment groups for patients who ovulated in either the intent to treat group or the group of patients who received hCG.

The secondary efficacy variable included rates of chemical pregnancy, clinical pregnancy and continuing pregnancy. There was a statistically significant difference in the proportion of patients with chemical pregnancy for Repronex S.C. compared with Repronex I.M.

The sponsor concluded that the three treatment regiments produced statistically comparable results for each of the primary and secondary efficacy variables. The Repronex S.C. group had a significantly higher rate of chemical pregnancies than Repronex I.M. These differences were, however, clinically small according to the sponsor.

The sponsor concluded that Repronex I.M. and S.C. were equal in effectiveness to each other and to Pergonal I.M. in terms of ovulation and pregnancy.

Reviewer's Efficacy Results

The sponsor claimed equal effectiveness between Repronex I.M. and Pergonal I.M., and between Repronex S.C. and Pergonal I.M. These claims are based on the lack of statistical significance between the investigational products and the active control. However, lack of statistical significance does not necessarily imply "therapeutic equivalence". Therefore this reviewers analysis focuses on 95% confidence intervals (adjusted for multiple comparisons) in order to help assess whether clinically important differences have been excluded.

Tables 8 and 9 present this reviewer's analysis of primary and secondary efficacy results for the intent-to-treat and primary responders groups. Therapeutic efficacy of Repronex I.M. and Repronex S.C. are compared to Pergonal I.M. on 1 cycle using the One-way ANOVA test. Ninety-five percent confidence intervals for differences between treatments were calculated. These confidence intervals were adjusted for multiple comparisons by the Sidak method.

Table 8
Review's Primary Efficacy Results of Study FPI Rep 97-01

Intent-to-Treat						
	N (%)			Adjusted P value		
N (%)	Repronex I.M.	Repronex S.C.	Pergonal I.M.	Diff (P –RI) • 95% CI on diff	Diff (P –RS) • 95% CI on diff	Diff (RI –RS) • 95% CI on diff
	N=36	N=36	N=36			
Ovulation	23 (63.9)	25(69.4)	21 (58.3)	.95 -.06* (-.3,.2)	.71 -.1* (-.4,.2)	.95 -.06** (-.3,.2)
Received hCG						
	N=25	N=27	N=21			
Ovulation	23 (92)	25(92.6)	21 (100)	.57 .08* (-.09,.2)	.62 .7* (-.09,.2)	1.0 -.01** (-.2,.2)

• P=Pergonal I.M., RI= Repronex I.M., RS=Repronex S.C.
* A positive difference favors Pergonal I.M.
** A positive difference favors Repronex I.M.

Table 9
Review's Secondary Efficacy Results of Study FPI Rep 97-01

	N (%)			Adjusted P value		
	Repronex I.M. N=36	Repronex S.C. N=36	Pergonal I.M. N=36	Diff (P –RI) • 95% CI on diff	Diff (P –RS) • 95% CI on diff	Diff (RI –RS) • 95% CI on diff
Intent-to-Treat						
	N=36	N=36	N=36			
Pts w/chemical pregnancy	4(11.1)	11 (30.6)	7(19.4)	.76 .08* (-.1,.3)	.56 -.1*(-.3,.1)	.12 -.2** (-.4,.03)
Pts w/clinical pregnancy	4(11.1)	6(16.7)	7(19.4)	.71 .08* (-.2,.2)	.98 .03* (-.2,.2)	.89 -.06** (-.3,.2)
Pts w/continuing pregnancy	4(11.1)	6(16.7)	7(19.4)	.71 .08* (-.2,.3)	.98 .03* (-.2,.2)	.89 -.06** (-.3,.2)
Received hCG						
	N=25	N=27	N=21			
Pts w/Chemical pregnancy	4(16)	11 (40.7)	7(33.3)	.49 .2* (-.2,.5)	.93 -.07* (-.4,.3)	.15 -.2** (-.6,-.06)
Pts w/Clinical pregnancy	4(16)	6(22.2)	7(33.3)	.44 .2* (-.1,.5)	.75 .1* (-.2,.4)	.94 -.06** (-.4,.2)
Pts w/Continuing pregnancy	4(16)	6(22.2)	7(33.3)	.44 .2* (-.1,.5)	.76 .1* (-.2,.4)	.94 -.06 **(-.4,.2)

• P=Pergonal I.M. , RI= Repronex I.M., RS=Repronex S.C.
* A positive difference favors Pergonal I.M.
** A positive difference favors Repronex I.M.

This reviewer's results agreed with the sponsor's results that there are no statistically significant differences in the primary efficacy variables of patients who ovulated in either the intent-to-treat or "received hCG" analyses on one cycle. However, there is no statistically significantly difference with chemical pregnancies in the intent-to-treat group for Repronex S.C. compared to Repronex I.M after adjustment for multiple comparisons.

The confidence intervals in Tables 8 and 9 must be examined by the medical reviewer to determine their clinical significance.

In this study patients had multiple pregnancies are summarized in Table 10; these differences were not statistically significant.

Table 10
Multiple Pregnancies

	Repronex I.M. N=2	Repronex S.C. N=3	Pergonal I.M. N=5
Twins	0 (0)	1 (33.3)	3 (60)
Triplets	2 (100)	0 (0)	1 (20)
Quadruplets	0 (0)	2 (66.7)	1 (20)

Source: Volume 8H1 of 24, page 41, Table 10

Conclusion

In study FPI Rep 97-02 and FPI Rep 97-01:

1. This reviewer's analysis is in agreement with the claim of the sponsor that there is no significant difference in the primary efficacy variable between Repronex and Pergonal I.M. for both studies.
2. This reviewer's analysis of the secondary efficacy variables showed no statistically difference between Repronex and Pergonal I.M. for either study. This finding is not in agreement with the sponsor's claim that there were significant statistically differences favoring for patients with continuing pregnancies in study FPI Rep 97-02 and for chemical pregnancies in study FPI Rep 97-01 after adjustment for multiple comparisons.
3. The sponsor claimed equal effectiveness between Repronex I.M. and Pergonal I.M., and between Repronex S.C. and Pergonal I.M. These claims are based on the lack of statistical significance between the investigational products and the active control. However, lack of statistical significance does not necessarily imply "therapeutic equivalence": Therefore, this reviewer's analysis compute 95% confidence interval based on the Sidak multiple comparison method. The confidence intervals must be examined by the medical reviewer to determine their clinical significance.

/S/

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