CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-765

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:	21-765 / 000
Drug Name:	Gonal-f (follitropin alfa for injection, recombinant human follicle stimulating hormone (r-FSH))
Indication(s):	Induction of ovulation and pregnancy in anovulatory infertile female patients in whom the cause of infertility is functional and not due to primary ovarian failure, and development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology program.
Applicant:	Serono, Inc.
Date(s):	Letter Date: May 23, 2003 PDUFA Date: March 26, 2004
Review Priority:	1S
Biometrics Division:	Division of Biometrics 2, HFD-715
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Michael Welch, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products, HFD-580
Clinical Team:	Audrey Gassman, M.D., Medical Reviewer Shelley Slaughter, M.D., Team Leader
Project Manager:	Archana Reddy
Key Words:	Clinical studies, NDA review, non-inferiority, Hodges-Lehman estimates

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The submitted data and analyses for one study in infertile women undergoing Assisted Reproductive Technology programs and one study in oligoanovulatory infertile women undergoing ovulation induction provide evidence to demonstrate the efficacy of the new formulation of Gonal-f® in these groups of women aged 18 to 39 years.

1.2 Background

This submission is in response to Approvable letters sent to the Sponsor (dated 21 Dec 2001 and 28 Feb 2002) for two supplements (S015 and S016) for the new Gonal-f® formulation. The Biopharmacologist's comments that the new Gonal-f® was not bioequivalent to the approved Gonal-f® were inadvertently not relayed to the Sponsor. The Sponsor was subsequently informed at a pre-NDA teleconference on 11 Dec 2002 of the Division's conclusion that the new Gonal-f® formulation was not bio-equivalent to the currently marketed Gonal-f® formulation. A letter stating the Division's position that the two Gonal-f® formulations were not bioequivalent was sent to the Sponsor on 26 Mar 2003.

The lack of bioequivalence between the two Gonal-f® formulations was discussed in detail at a subsequent meeting with the sponsor held on 5 May 2003. At the meeting, the Sponsor proposed submission of two completed clinical studies (studies 21884 and 22240) to demonstrate efficacy and safety of the new Gonal-f® formulation. These two clinical studies would use clinical endpoints to demonstrate that the new Gonal-f® was non-inferior to currently approved FSH products for each of the female indications (ovulation induction and use in subjects undergoing Assisted Reproductive Technology procedures). The Division agreed to evaluate the two Phase 3 clinical studies, which were submitted electronically on 27 May 2003.

This submission for the new Gonal-f® formulation is for the following indication:

> *Gonal-f® (follitropin alfa for injection) is indicated for the induction of ovulation and pregnancy in the oligoanovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure. Gonal-f® is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program.*

1.3 Statistical Issues and Findings

Statistical issues for Study 21884 are as follow:

- The Sponsor included the approved Gonal-F group in the primary analysis ANOVA model even though the primary comparison is between the new Gonal-F formulation and Fertinex. This reviewer's analysis does not include the approved Gonal-F group because its inclusion may reduce the variance of the difference estimate and thus shorten the length of the confidence interval.
- The Sponsor calculated a one-sided 95% confidence interval to determine the lower bound for comparison to the superiority and non-inferiority thresholds. This reviewer instead calculated a two-sided 95% confidence interval.
- This reviewer found that the distribution of the number of fertilized oocytes per subject is not normally distributed, so a non-parametric method (Hodges-Lehman estimates) is used to analyze the data.

Statistical issues for Study 22240 are as follow:

- The Sponsor amended the protocol twice, neither of which was submitted to the Division for review.
- The original primary study objectives were to evaluate: 1) the equivalence of new Gonal-f to approved Gonal-f and 2) [redacted] In the amended protocol, the primary study objective is to evaluate the non-inferiority of new Gonal-f to approved Gonal-f.
- The Sponsor uses a one-sided 95% confidence interval for the primary efficacy analysis. This reviewer is using the original protocol specified two-sided 97.5% confidence interval.
- This reviewer used the new Gonal-f and approved Gonal-f groups to calculate simple rates and variance estimates for each group instead of using all three treatment groups in a logistic regression model as used by the Sponsor.

Study 21884 in infertile women undergoing Assisted Reproductive Technology programs is statistically significant for the primary efficacy analysis with respect to the number of fertilized oocytes. Study 22240 in oligoanovulatory infertile women undergoing ovulation induction is statistically significant for the primary efficacy analysis with respect to ovulation rate in the first cycle of treatment. These results show evidence of efficacy for these groups of women of age 18 to 39 years.

2. INTRODUCTION

2.1 Overview

Treatment of infertility can range from ovulation induction followed by sexual intercourse or intrauterine insemination to assisted reproduction technologies (ART) with in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Both procedures require multiple follicular development to increase the number of oocytes, with more oocytes needed for ART than for ovulation induction.

The Sponsor has submitted two clinical studies in infertile female subjects, aged 18 to 39 years, for the new recombinant human follicle stimulating hormone (r-hFSH) Gonal-f® formulation. Study 21884 is in ovulatory infertile women undergoing ART (IVF or ICSI), and study 22240 is in oligoanovulatory infertile women in whom the cause of infertility is functional undergoing ovulation induction. Table 2.1 presents a brief summary of each of the two studies addressed in this review.

Table 2.1
Brief Summary of Clinical Studies for the New Formulation of Gonal-f

Study Number (Dates Conducted)	Number of Centers (Location)	Patient Population	Treatment	Number Treated	Design[1]	Duration of Treatment
21884 (July 2000 to June 2001)	34 (26 U.S., 6 Argentina)	Infertile women undergoing ART (IVT or ICSI), 18 to 39 yrs. of age	r-hFSH (new Gonal-f) Gonal-f Fertinex	237 237 237	AB, R, PG, MC	1 cycle
22240 (3-29-01 to 7-15-02)	36 (26 U.S., 10 Argentina)	Oligoanovulatory infertile women undergoing ovulation induction, 18 to 39 yrs. of age	r-hFSH (new Gonal-f) Gonal-f Fertinex	83 94 98	AB, R, MC	3 cycles

Source: Statistical Reviewer's listing.
[1] AB = Assessor-blind, R = Randomized, PG = Parallel Group, MC = Multicenter

The Sponsor has submitted this application for the new formulation of Gonal-f® for the following indication:

> *Gonal-f® (follitropin alfa for injection) is indicated for the induction of ovulation and pregnancy in the oligoanovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure. Gonal-f® is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) programs.*

2.2 Data Sources

The study reports, SAS data sets, and additional information for these two studies are submitted in four electronic format files and are located in the Electronic Document Room at:

\\CDSESUB1\N20378\S_032\2003-05-23
\\CDSESUB1\N20378\S_032\2003-07-22
\\CDSESUB1\N20378\S_032\2003-08-12
\\CDSESUB1\N20378\S_032\2004-01-09

One paper submission of a response to FDA request for information that includes the original and all amended protocols for study 22240 is dated 22 July 2003 and consists of 2 volumes.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study 21884

Study Design and Endpoints

This is a randomized, parallel group, multi-center, assessor-blind, Phase 3 study to compare the safety and efficacy of the new recombinant human follicle stimulating hormone (r-hFSH) Gonal-f formulation versus Fertinex for stimulation of follicular development in infertile women, 18 to 39 years of age, undergoing assisted reproduction technology (IVF or ICSI). The protocol stipulated that an estimated 223 evaluable patients are enrolled in each of the three study arms with up to a total of 700 patients randomized to account for patients who may be non-evaluable for oocyte number and quality and for drop-outs.

Infertile subjects who satisfy the protocol eligibility criteria are admitted and undergo one treatment cycle on an outpatient basis. All subjects undergo pituitary down-regulation with a gonadotropin-releasing hormone agonist prior to and during stimulation of multiple follicular development with one of the three study treatments. When pituitary down-regulation is confirmed, subjects are randomly allocated in a 1:1:1 ratio to each hFSH treatment (new Gonal-f, Fertinex, approved Gonal-f) using a computer-generated centralized randomization procedure. Randomization is stratified according to center number, age of the patient (using two age-dependent starting dosage regimens for hFSH – 18 to 34 years and 35 to 39 years), and method of insemination (IVF or ICSI) to be used. Only the study nurse/coordinator and/or the pharmacist/pharmacy assistant and the subject are aware of the subject's randomized hFSH treatment arm while the assessing physician, ultrasonagrapher, and other members of the research team remain blinded to treatment allocation. Each hFSH treatment is administered daily via subcutaneous injection until multiple follicular growth and development is adequate, as assessed by ovarian ultrasound and serum estrogen levels. Oocytes are retrieved approximately 34-36 hours after Profasi (u-hCG) administration (to induce final follicular maturation) and then are assessed and fertilized in vitro via regular insemination or ICSI.

The primary efficacy endpoint is the number of fertilized oocytes observed on the day of fertilization. The primary objective is to Also to be considered in the statistical analyses is the alternative to support the non-inferiority of the new Gonal-f formulation compared to Fertinex.

Statistical Methodologies

The Sponsor analyzes the total number of fertilized oocytes per subject using a 4-way analysis of variance model (ANOVA) with effects for treatment, center, age and method of insemination strata. The reviewer does not agree with keeping the approved Gonal-f group in the ANOVA model because inclusion of the approved Gonal-f group may reduce the variance of the difference estimate and thus shorten the length of the derived confidence interval. So, this reviewer will not include approved Gonal-f in the analysis described below.

Non-inferiority of the newly formulated Gonal-f to Fertinex is demonstrated if the lower limit of the one-sided 95% confidence interval of the difference is greater than or equal to -1 fertilized oocyte. The Sponsor presents an equivalent lower bound for a one-sided 95%confidence interval, the lower bound of a two-sided 90% confidence interval, for their results (see Table 3.3 below).

Both the Sponsor and this reviewer excluded subjects who did not complete the study and subjects who had mixed inseminations, both IVF and ICSI, from the efficacy analysis. The numbers of patients with this classification are 7 in the new Gonal-f group and 11 in the Fertinex group. This reviewer performed an additional analysis of all treated subjects, regardless if they had mixed inseminations or if they had fertilized oocytes or not (if not, then the number is zero). This is the intent-to-treat analysis.

This reviewer found that the count data for the number of fertilized oocytes is not symmetrically distributed, let alone normally distributed. In the Appendix, Figure 1 displays the stem-and-leaf diagrams and Figure 2 displays histograms of the raw data for each treatment group. To analyze the data, this reviewer uses the Hodges-Lehman procedure, which utilizes medians to calculate the exact Hodges-Lehmann confidence interval for the difference between the medians of the raw distributions. Also, a two-sided 95% confidence interval is calculated instead of a one-sided 95% confidence interval as done by the Sponsor. A two-sided 95% confidence interval is what the Division requires for the comparisons made in this submission. This reviewer uses the lower bound of this confidence interval to compare to the non-inferiority threshold values described above.

Subject Disposition, Demographic and Baseline Characteristics

Table 3.1 presents a summary of subject disposition. In the Fertinex group, two subjects who were randomized did not receive study treatment. In both groups, more than 94% of treated subjects completed treatment. The main reason for discontinuation is not receiving hCG treatment, followed by not undergoing ovum pick up and not having Day 1 fertilization assessed.

Table 3.1
Study 21884: Summary of Subject Disposition

	New Gonal-f	Fertinex
Study 21884 (U.S., Argentina)		
Randomized	237	239
Treated (ITT)	237	237
Completed*	223 (94.1)	229 (96.6)
All Discontinuations* n (%)	14 (5.9)	8 (3.4)
Did not receive hCG treatment**	*10 (71.4)*	*7 (87.5)*
Did not undergo ovum pick up (IUI)**	*2 (14.3)*	
Did not have Day 1 fertilization assessed**	*2 (14.3)*	*1 (12.5)*

Source: Figure 1 on page 48 in Study 21884 report.
* With respect to number of treated subjects.
** With respect to number of all discontinuations.

Table 3.2 presents some demographic and baseline characteristics for the treated population. Both treatment groups are similar with respect to age, race distribution, and type of infertility.

Table 3.2
Study 21884: Demographic and Baseline Characteristics

	New Gonal-f (N=237)	Fertinex (N=239)
Age (yrs)		
Mean (s.d.)	32.5 (3.7)	32.7 (3.5)
Race n (%)		
White	195 (82.3)	200 (83.7)
Black	16 (6.7)	9 (3.8)
Asian	4 (1.7)	6 (2.5)
Other	22 (9.3)	24 (10.0)
Type of Infertility n (%)		
Primary	130 (54.8)	131 (54.8)
Secondary	107 (45.2)	108 (45.2)

Source: Prepared by Statistical Reviewer from SAS data sets provided by the Sponsor.

Results and Conclusions

Table 3.3 presents the Sponsor's results for the number of fertilized oocytes. The Sponsor concludes that the new Gonal-f is non-inferior to Fertinex with respect to the number of fertilized oocytes.

Table 3.3
Study 21884: Sponsor's Results for the Number of Fertilized Oocytes

	New Gonal-f (N=216)	Fertinex (N=218)	Treatment Difference (Two-sided 90% C.I.)*
Number of fertilized oocytes			
Mean (s.d.)	6.7 (4.1)	6.0 (3.7)	0.74 (0.11, 1.36)
Median (min, max)	6 (0, 22)	5 (0, 18)	

Source: Sponsor Tables 31 and 33,pages 75 and 77 of Study 21884 report.
*Treatment difference and 2-sided 90% confidence interval based on 4-way ANOVA with effects for treatment (new Gonal-f, approved Gonal-f, and Fertinex), center, age, and method of insemination strata.

Table 3.4 presents this reviewer's results for the number of fertilized oocytes. Based on a non-parametric analysis and using a two-sided 95% confidence interval, this reviewer concluded that both analyses demonstrate that the new Gonal-f formulation is non-inferior to Fertinex with respect to the number of fertilized oocytes.

Table 3.4
Study 21884: Reviewer's Results for the Number of Fertilized Oocytes

	New Gonal-f	Fertinex	Treatment Difference (Two-sided 95% C.I.)*
Number of fertilized oocytes			
N	216	218	
Median (min, max)	6 (0, 22)	5 (0, 18)	1 (0,1)
Mean (s.d.)	6.7 (4.1)	6.0 (3.7)	0.7 (-0.04, 1.4)
ITT Analysis			
N	237	237	
Median (min, max)	6 (0, 22)	5 (0, 18)	1 (0,1)
Mean (s.d.)	6.3 (4.3)	5.9 (3.9)	0.4 (-0.3, 1.2)

Source: Prepared by Statistical Reviewer from SAS data sets provided by the Sponsor.
* Median treatment difference and two-sided 95% confidence interval based on the Hodges-Lehmann estimate for treatment difference.

3.1.2 Study 22240

Study Design and Endpoints

This is a randomized, parallel group, multi-center, assessor-blind, Phase 3 study to compare the safety and efficacy of the new recombinant human follicle stimulating hormone (r-hFSH) Gonal-f formulation versus the approved Gonal-f in oligoanovulatory infertile women, aged 18 to 39 years, in whom the cause of infertility is functional undergoing ovulation induction.

Subjects are screened for entry the cycle prior to the anticipated start of treatment. Within 3days after menses onset, a baseline ultrasound is performed and a blood sample is collected. Subjects who are ready to begin treatment are randomized to one of three hFSH treatment arms: new Gonal-f, Fertinex, or approved Gonal-f. Stimulation and development of follicles with hFSH begins between cycle days 3 to 5, inclusive. Subjects return to the clinic on treatment day 6 for ultrasound and estradiol monitoring. Stimulation monitoring is repeated every two to three days after treatment day 6 until a significant ovarian response is seen. Once a lead follicle reaches a mean diameter of 14 mm, subject visits are scheduled every one or two days. Human chronionic gonadotropin (hCG) hormone, to help the egg mature (final follicular maturation), is administered when at least one follicle, but no more than three, has reached a mean diameter ≥17 mm and estradiol levels are within acceptable limits. Once mature, the subject has either intercourse or intrauterine insemination to fertilize the oocytes produced. All subjects receive three cycles of treatment but only the first cycle of treatment is used for the primary efficacy analysis.

The original protocol, which the Division reviewed, is dated Nov. 22, 2000. Amendment 1 is dated Aug. 6, 2001 and Amendment 2 is dated Oct. 22, 2001. An information request from the Division was sent to the Sponsor to verify if the amendments were submitted and to provide the submission dates. The Sponsor replied that:

> Due to an administrative oversight, the two protocol amendments were not submitted to the IND (Volume 1, page 7, submission dated July 22, 2003).

In addition, the Sponsor states in the amended protocol that:

> Based upon findings from a recently completed sister study [study 21884], an executive decision was made to revise the current study objectives for Protocol 22240. The amended protocol now emphasizes the non-inferiority of the new formulation of r-hFSH compared to Gonal-f. (CLINICAL STUDY PROTOCOL AMENDMENT NO. 2 (Date of Amendment 2, Oct. 22, 2001), Section 1.1, Volume 2, page 072, submission dated July 22, 2003)

Originally, the primary study objectives were to evaluate: 1) the equivalence of new Gonal-f to approved Gonal-f and 2) [redacted]. Now in the amended protocol, the primary study objective is to evaluate the non-inferiority of new Gonal-f to approved Gonal-f. Based on the above information, the Division decided that they would hold the Sponsor to the original protocol for the comparison of the two Gonal-f formulations, which the Division reviewed.

The primary efficacy endpoint is the ovulation rate in the first treatment cycle between the new Gonal-f formulation and the approved Gonal-f, defined as the number of patients who ovulate (mid-luteal serum progesterone level (P_4)

≥ 10 ng/mL) divided by the total number of patients. The Sponsor assumed ovulation has occurred in any patient who becomes pregnant even though the P_4 serum level is below the above criterion, or is missing.

Based on advice from the Medical Reviewer, ovulation is defined by a single mid-luteal serum P_4 level ≥ 10 ng/mL or by a livebirth or by a heartbeat in this reviewer's analysis.

Statistical Methodologies

In the original protocol, the ovulation rate is analyzed by logistic regression analysis with effects for treatment and center. In the amended protocol, the same logistic regression analysis to compare the new Gonal-f to the approved Gonal-f is planned. The Sponsor states that the Fertinex comparisons will not be made even though the Fertinex treatment arm will be included in the logistic regression modeling. The reviewer does not agree with keeping the Fertinex group in the logistic regression model because inclusion of the Fertinex group may reduce the variance of the difference estimate and thus shorten the length of the derived confidence interval. So, this reviewer will not include Fertinex in the analysis described below.

The confidence interval (C.I.) is based on estimates from the logistic regression model. In the original protocol, the two treatments are deemed equivalent if the 97.5% two-sided C.I. for the difference in ovulation rates between the new Gonal-f and the approved Gonal-f is between – 20% and 20%, inclusive, in the first cycle of treatment. In the amended protocol, the two treatments are deemed non-inferior if the lower bound of the 95% one-sided C.I. for the difference in ovulation rates between the new Gonal-f and the approved Gonal-f is greater than or equal to –20% in the first cycle of treatment.

All patients who receive at least one injection of randomized hFSH treatment will be included in the Intent-to-Treat (ITT) population for ovulation rates. In addition, centers with fewer than six treated patients are pooled by geographic location.

The Sponsor amended the protocol without submitting it to the Division for review and uses a one-sided 95% confidence interval for the primary efficacy analysis. This reviewer is using the original protocol specification of a two-sided 97.5% confidence interval. In addition, this reviewer only used the new Gonal-f and approved Gonal-f groups to calculate simple rates for each group.

Table 3.5 presents a comparison of the estimated sample sizes for the original and amended protocols. Subjects are randomized in a 1:1:1 ratio and stratified by center. The original protocol called for 519 subjects (173 per group) to be enrolled while the amended protocol now calls for 240 subjects (80 per group) to be enrolled.

Table 3.5
Study 22240: Assumptions Used for Sample Size Estimates for the Comparison of the New Gonal-F to the Approved Gonal-f

Protocol	No. of Comparisons to new Gonal-f	Hypothesis	Assumed Ovulation Rate	C.I. for Hypothesis on Difference	1- or 2-sided C.I.	Signif. Level (C.I. size)	Power	N (n/grp.)	Total N, Accounting for Drop-outs
Original, reviewed by Division	2	Equivalence	64%	Difference between -20% and 20%, inclusive	2-sided	0.025 (0.975)	≈94%	519 (173)	519
Amended, not reviewed by Division	1	Non-inferiority	64%	Difference greater than or equal to -20%	1-sided	0.05 (0.95)	≈80%	216 (72)	240

Source: Statistical Reviewer's listing.

Patient Disposition, Demographic and Baseline Characteristics

Table 3.6 presents a summary of subject disposition in cycle 1 of treatment. All treated subjects completed the first cycle of treatment.

Table 3.6
Study 22240: Summary of Subject Disposition in Cycle 1

	New Gonal-f	Approved Gonal-f
Study 22240 (U.S., Argentina)		
Randomized	84	95
Treated (ITT)	83	94
Completed*	83 (100)	94 (100)

Source: Figure 1 on page 36 in Study 22240 report.
* With respect to number of treated subjects.
** With respect to number of all discontinuations.

Table 3.7 presents some demographic and baseline characteristics for the treated population. Both treatment groups were similar in race distribution and type of infertility. However, there was a difference in age. The age of subjects in the new Gonal-F group was about one year younger than the age of subjects in the approved Gonal-f group.

Table 3.7
Study 22240: Demographic and Baseline Characteristics

Characteristic	New Gonal-f (N=84)	Approved Gonal-f (N=95)
Age (yrs)		
Mean (s.d.)	29.2 (3.9)	30.7 (3.6)
Race n (%)		
White	67 (79.8)	79 (83.2)
Black	5 (5.9)	6 (6.3)
Asian	3 (3.6)	2 (2.1)
Other	9 (10.7)	8 (8.4)
Type of Infertility n (%)		
Primary	50 (59.5)	56 (59.0)
Secondary	34 (40.5)	39 (41.0)

Source: Prepared by Statistical Reviewer from SAS data sets provided by the Sponsor.

Results and Conclusions

Table 3.8 presents the Sponsor's ovulation rate results based on the amended protocol. The Sponsor concludes that the new Gonal-f is non-inferior to the approved Gonal- F for ovulation rate after one cycle of treatment.

Table 3.8
Study 22240: Sponsor's Results for Ovulation* Rate in the First Cycle (ITT Population)

	New Gonal-f (N=83)	Approved Gonal-f (N=94)	Lower Limit of One-sided 95% C.I.**
Number ovulated (%)	60 (72.3)	65 (69.1)	-0.056

Source: Sponsor Table IMP22240-24 on page 92 of Study 22240 report.
* Ovulation is defined by a single mid-luteal serum progesterone level ≥ 10 ng/mL or if patient became pregnant in the cycle.
** One-sided 95% confidence interval based on a logistic regression model with effects for treatment (new Gonal-f, Gonal-f, and Fertinex) and center.

Table 3.9 presents the reviewer's result for ovulation rate based on the original protocol. This reviewer concludes that the new Gonal-f formulation is equivalent to the approved Gonal-f formulation for ovulation rate after one cycle of treatment.

Table 3.9
Study 22240: Reviewer's Results for Ovulation* Rate in the First Cycle (ITT Population)

	New Gonal-f (N=83)	Approved Gonal-f (N=94)	Two-Sided 97.5% C.I. **
Number ovulated (%)	59 (71.1)	64 (68.1)	(-0.13, 0.18)

Source: Prepared by Statistical Reviewer from SAS data sets provided by the Sponsor.
* Ovulation is defined by a single mid-luteal serum progesterone level ≥ 10 ng/mL or by a livebirth or by a heartbeat.
** Two-sided 97.5% confidence interval based on the standardized statistic and inverting two 1-sided tests using StatXact.

3.2 Evaluation of Safety

There is no statistical evaluation of safety necessary for this review. For information, reference the clinical review evaluation of safety section.

4.0 FINDINGS IN SUBGROUP POPULATIONS

The subgroup populations of interest are age group (less than 35 years of age and greater than or equal to 35 years of age) and method of insemination performed (IVF or ICSI). According to the Medical Reviewer, these are of interest with respect to labeling and are addressed in the clinical review evaluation of efficacy section.

5.0 CONCLUSIONS

Study 21884 in infertile women, aged 18 to 39 years, undergoing Assisted Reproductive Technology programs demonstrated that the new Gonal-f formulation is non-inferior to Fertinex with respect to the number of fertilized oocytes. Study 22240 in oligoanovulatory infertile women, aged 18 to 39 years, undergoing ovulation induction demonstrated that the new Gonal-f formulation is equivalent to the approved Gonal-f formulation for ovulation rate after one cycle of treatment.

APPENDIX

Figure 1
Study 21884: Stem and Leaf Diagrams of the Number of Fertilized Oocytes by Treatment Group

Fertinex Number of Fertilized Oocytes

N = 218 **Median = 5**
Quartiles = 3, 8

Decimal point is at the colon

Count	
7	0 : zzzzzzz
6	1 : 000000
13	2 : 0000000000000
32	3 : 00000000000000000000000000000000
34	4 : 0000000000000000000000000000000000
21	**5 : 000000000000000000000**
24	6 : 000000000000000000000000
19	7 : 0000000000000000000
18	8 : 000000000000000000
10	9 : 0000000000
8	10 : 00000000
5	11 : 00000
8	12 : 00000000
2	13 : 00
3	14 : 000
4	15 : 0000
0	16 :
2	17 : 00
2	18 : 00

New Gonal-f Number of Fertilized Oocytes

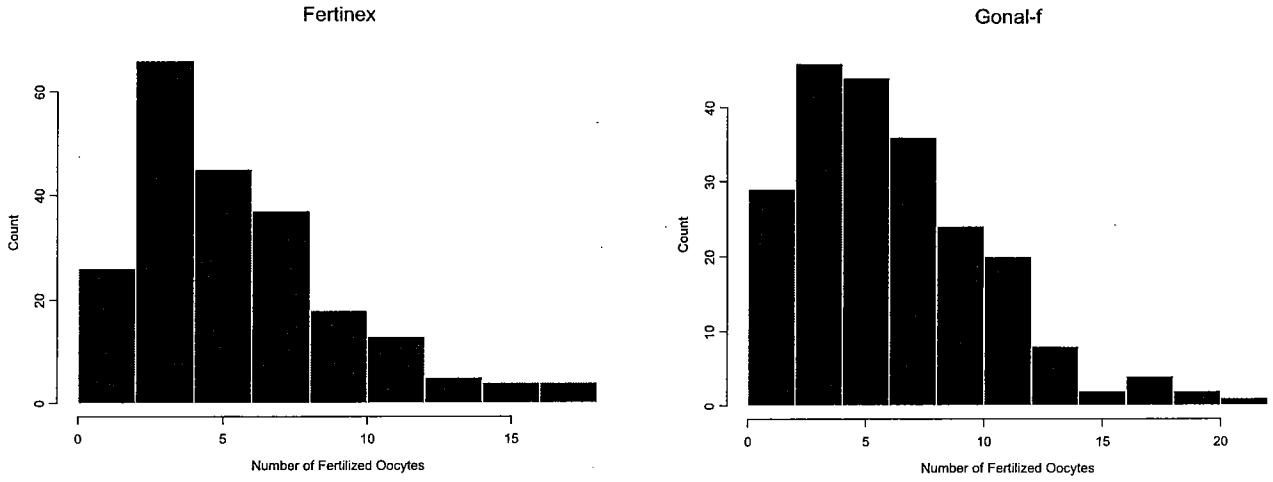
N = 216 **Median = 6**
Quartiles = 4, 9

Decimal point is at the colon

Count	
5	0 : zzzzz
9	1 : 000000000
15	2 ; 000000000000000
19	3 : 0000000000000000000
27	4 : 000000000000000000000000000000
25	9 5 : 00000000000000000000000000
19	**6 : 000000000000000000**
16	7 : 0000000000000000
20	8 : 00000000000000000000
13	9 : 0000000000000
11	10 : 00000000000
3	11 : 000
17	12 : 00000000000000000
3	13 : 000
5	14 : 00000
2	15 : 00
0	16 :
3	17 : 000
1	18 : 0

High: 20 20 22

Figure 2
Study 21884: Histograms of the Number of Fertilized Oocytes by Treatment Group



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Mike, please sign off today, Wednesday, and let Ed
know to please sign off on it today
as well. Thanks, Sonia.

Mike Welch
3/17/04 11:38:19 AM
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Concur with review.
Ed, Needs to be signed off today.

S. Edward Nevius
3/17/04 11:47:32 AM
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Concur with review.