CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-765

MEDICAL REVIEW(S)

TRADENAME (follitropin alfa for injection)
Division Director Memorandum

NDA:	**21-765 (initial submission as 20-378/S-032)**
Drug:	**Tradename (follitropin alfa for injection)**
Indication:	**1. Development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program.** **2. Induction of ovulation and pregnancy in oligo-anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure.**
Dosage/Form/Strength:	**Each r-hFSH Single Dose vial is filled with r-hFSH in a lyophilized powder to deliver 37.5 IU (2.8 µg), 75 IU (5.5 µg) or 150 IU (11 µg) of r-hFSH, respectively. Single dose vials are reconstituted with Sterile Water for Injection, USP.**
Applicant:	**Serono, Inc**
Original Receipt Date:	**May 27, 2003**
Review Completed:	**March 24, 2004**
Date of Memorandum:	**March 25, 2004**

I concur with Dr. Slaughter's Team Leader Memorandum for NDA 21765, dated March 25, 2004.

Daniel Shames, M.D.
Division Director, HFD-580
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/s/

Daniel A. Shames
3/25/04 04:04:56 PM
MEDICAL OFFICER

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Team Leader Review

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Background

Gonal-f® was approved by the Agency on September 29, 1997 for the indications of development of multiple follicles (controlled ovarian stimulation) in ovulatory patients participating in an Assisted Reproductive Technology program and induction of ovulation in the anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure. The original formulation for Gonal-f® is a lyophilized formulation (filled by IU) for reconstitution with water for injection. As part of a Phase 4 commitment to ensure stability of the product, the Sponsor modified the original formulation by adding — methionine and polysorbate 20 as ——— This revised formulation was manufactured using fill-by-mass technology. To link the filled-by-mass revised formulation to the original formulation filled-by-IU formulation, the Sponsor conducted two clinical pharmacology studies, IMP 218159 and 22596, to demonstrate bioequivalence. These studies were submitted to NDA 20-378/S-015. However upon review by the Office of Clinical Pharmacology and Biopharmaceutics, the two formulations were determined not to be bioequivalent and Supplement 15 was found to be Approvable.

At a May 5, 2003 meeting with the Division, the Sponsor proposed submission of two previously completed clinical studies in women to support approval for the filled-by-mass revised formulation. The sponsor also requested to concurrently submit an application for a liquid

formulation of follitropin alfa (filled-by-mass) to be supported by bioequivalence (Study 23572) of the liquid filled by mass formulation to the lyophilized filled-by-mass revised formulation of follitropin alfa. The Sponsor was told that they could do so at their own risk in that the outcome of the application for the liquid formulation of follitropin alfa would be dependent upon a successful outcome (approval) of the lyophilized filled-by-mass revised formulation.

The application for the liquid formulation (filled-by-mass) of follitropin alfa was submitted on July 29, 2003 supported by a single bioequivalence study, Study 23572, comparing the liquid filled by mass formulation of follitropin alfa with the lyophilized filled-by-mass revised formulation of follitropin alfa. A Not-Approvable recommendation for the Gonal-f® pen, NDA 21-684, was taken on November 25, 2003 just before the 4-month PDUFA goal date. The Not-Approvable recommendation was made because the reference drug product, the lyophilized filled-by-mass revised formulation of follitropin alfa (subsequently referred to in this review as the revised formulation of follitropin alfa), the subject of this application, NDA 21-765, was still under review and not an approved drug product. In addition, Division of Scientific Investigation inspections of the single clinical site for bioequivalence trial, Study 23572, had not been completed.

NDA 21-765 (submitted as NDA 20-378/S-032), containing the clinical data from Studies 21884 and 22240 (two Phase 3 non-inferiority studies to support the indications of multiple follicular development for IVF and ovulation induction, respectively) for the revised formulation of follitropin alfa was submitted electronically and received on May 27, 2004.

Regulatory History

According to the interim guidance, dated July 12, 1993 and titled, " Separate Marketing Applications and Clinical Data for purposes of Assessing User Fees under The Prescription Drug User Fee Act of 1992" (Attachment E -PDUFA)", differences in excipients that require separate clinical studies of safety or effectiveness should not be included in the same original application. The revised formulation of follitropin alfa for injection (containing methionine and polysorbate 20 and filled by mass) submitted under NDA 20-378/ S-032 was not bioequivalent to the original formulation of Gonal-f® (NDA 20-378) and because of lack of bioequivalence, Phase 3 clinical trial information was submitted (and required) to support the application for this new formulation for the indications of ovulation induction and multiple follicular development in ART for infertile women. Following the recommendations of the above cited policy, the Sponsor was told that the clinical trial information supporting the revised formulation of follitropin alfa for injection could not be reviewed as an efficacy supplement to NDA 20-378 (for the original formulation of Gonal-f®). The Sponsor was presented with two options for proceeding with review: Option 1. The Division would administratively create a new NDA for review of the clinical trial information for the revised formulation of follitropin alfa for injection. Also required under this option would be to remove from NDA 20-378/S-015, the request for approval of revised formulation of follitropin alfa for injection. The new NDA could then reference NDA 20-378/S-015 for the supporting chemistry information. Option 2.

The Sponsor elected to proceed with option 1. NDA 21-765 was assigned for the review of the lyophilized filled-by-mass revised formulation of follitropin alfa.

Clinical Efficacy and Safety

Two clinical studies were submitted to support this application, Study 22240 (for an ovulation induction indication) and Study 21884 (for an indication of multiple follicular development in ART).

Study 22240

Efficacy
Study 22240, titled "A phase III, prospective, randomized, assessor blind, multi-center, multinational comparative trial of a new formulation of r-hFSH versus Fertinex® and Gonal-f® in oligo-anovulatory infertile women undergoing ovulation induction", was submitted to IND 38,712 on February 20 2001. The original protocol for Study 22240 included co-objectives of confirming [redacted] the clinical equivalence of the revised formulation of follitropin alfa to Gonal-f®. The Sponsor made two significant amendments (Protocol Amendments dated August 6, 2001 and October 22, 2001) to the original protocol. The [redacted] was deleted from the study and the required sample size was reduced. The need for clomiphene-resistance was eliminated, patients with fasting insulin levels up to 25 microunits/ml (instead of the previous normal insulin level requirement) and use of insulin-sensitizing agents were allowed in the study. These Amendments were not submitted to, received or reviewed by the Division. The elimination of the requirement for clomiphene resistance, the inclusion of subjects with some degree of insulin resistance and the use of insulin-sensitizing agents had the impact of altering the treated population of oligo-anovulatory patients.

Study 22240 was a prospective, randomized, assessor-blind, multi-national, multi-center (36 centers throughout the United States and Argentina), comparative study that recruited oligo–anovulatory infertile women undergoing ovulation induction. With the exception of the inclusion of women with insulin resistance and women on insulin-sensitizing agents, the other enrollment criteria were all felt to be appropriate. Within three days after menses subjects were randomized on a 1:1:1 ratio to receive the revised formulation of follitropin alfa, Gonal-f® or Fertinex®. Per the original protocol, efficacy was to be demonstrated if the ovulation rate for patients treated with the revised formulation of follitropin alfa minus the ovulation rate for patients treated with Gonal-f® is between –20% and 20% inclusive, in the first cycle of treatment.

The Sponsor's analysis (see Table 1 from Statistical reviewer's Table 3.8) follows the statistical plan in the amended protocol.

Table 1. Sponsor's Analysis of Ovulation Rate in the First Cycle of Treatment for Study 22240, ITT Population [a]

	Revised formulation of follitropin alfa (N=83)	Gonal-f® (N=94)	Lower limit of one-sided 95% C.I. [c]
Number and percent ovulated [b]	60 (72.3)	65 (69.1)	-0.056

[a]Source: Statistical reviewer table 3.8, Sponsor Table IMP22240-24 of Study 22240 report
[b]Ovulation is defined by a single mid-luteal serum progesterone level ≥ 10 ng/ml or pregnancy
[c]One-sided 95% CI based on a logistic regression model with effects for treatment (revised formulation of follitropin alfa, Gonal-f® and Fertinex®

Because the Division did not have the amended protocols for review, the Division analyzed the study according to the original statistical protocol (see Table 2).

Table 2. Division's Analysis of Ovulation Rate in the First Cycle of Treatment for Study 22240, ITT Population [a]

	Revised formulation of follitropin alfa (N=83)	Gonal-f® (N=94)	Two-Sided 97.5% C.I [c].
Number and percent ovulated	59 (71.1)	64 (68.1)	(-0.13, 0.18)

[a]Source: Statistical reviewer table 3.9 (prepared from SAS data sets provided by the Sponsor)
[b]Ovulation is defined by a single mid-luteal serum progesterone level ≥ 10 ng/ml or fetal sac and heartbeat
[c]Two-sided 97.5% CI based on the standardized statistic and inverting two 1-sided tests using StatXact.

In the assessment of the primary efficacy endpoint of rate of ovulation, both the analysis performed by the Sponsor and that of the Division demonstrate non-inferiority of the revised formulation of follitropin alfa compared to Gonal-f®.

As stated the Sponsor amended the original protocol to include women with insulin resistance and women taking insulin-sensitizing agents. The Division did not have a chance to review and comment on these changes. Seven (7) of 95 subjects (7.4% of subjects) in the Gonal-f® group were treated with concomitant insulin-sensitizing therapy, while 7 of 84 subjects (8.3%) in the revised formulation of follitropin alfa group were treated with concomitant insulin-sensitizing therapy. The patients treated with insulin sensitizing agents appear to be equally distributed between the two groups. Insulin-sensitizing agents have been widely reported in the literature to improve the rate of ovulation when used with gonadotropins. It is expected that their use impacted the observed rates of ovulation. The inclusion of insulin-resistant women (elevated fasting insulin) as well as use of insulin-sensitizing agents is a significant departure from the enrollment criteria for previous gonadotropin products assessed and approved by the Agency.

The clinical pregnancy rate was a secondary variable. Clinical pregnancy in this study was defined by the presence of a fetal sac with or without a fetal heartbeat. The clinical pregnancy rate for the first treatment cycle was 27.7 % in the revised formulation of follitropin alfa group and 19.1% in the Gonal-f group. The study was not powered to detect difference in clinical pregnancy rates.

Safety

The rate of adverse events across all treatment arms were similar (63.3% in Fertinex®, 60.2%-revised formulation of follitropin alfa and 66% in Gonal-f®. The most commonly reported adverse events were headache and abdominal pain.

There were no deaths in Study 22240. In the revised formulation of follitropin alfa there was 1 patient with a ruptured ectopic pregnancy, 2 spontaneous abortions, and 3 premature deliveries. The rate of ovarian hyperstimulation syndrome was 4.6% in the revised formulation of follitropin alfa; this included 1 case of moderate-to-severe ovarian hyperstimulation syndrome. The overall pregnancy-related adverse events and the rate of ovarian hyperstimulation syndrome, as well as other serious adverse event, were similar across all treatment groups and no obvious safety concerns were noted in the Medical Officer' safety review.

Study 21884

Efficacy

Study 21884, titled "A phase III, multi-center, multi-national, randomized, assessor blind study to compare the safety and efficacy of a new formulation of recombinant human FSH (r-hFSH) versus Fertinex® versus Gonal-f® in stimulating multiple follicular development prior to ART in patients pretreated with GnRH agonist", was submitted to IND 38,712 on March 20, 2000. The objective of this protocol was to

The introductory letter submitted with the protocol stated the Sponsor's intention to conduct Study 21884 in parallel with the bioequivalence trial(s), (Studies IMP 218159 and IMP 22596), in the event that the Sponsor was unable to demonstrate bioequivalence of the revised formulation of follitropin alfa to Gonal-f® and to update the package insert with more current and relevant clinical data. The protocol was amended on August 9, 2000 (received August 10, 2000). The final amended protocol for study 21884 included a co-objective of confirming via a "step-down" approach the non-inferiority of the revised formulation of follitropin alfa and Fertinex®

ıe Statistician and Primary Medical Officer reviews concurred that the "step-down" approach in the Protocol Amendment was acceptable. Per the accepted final amended protocol,

Non-inferiority of the revised formulation of follitropin alfa and Fertinex® will be declared if the lower limit of the 95% C.I. of the difference [revised formulation of follitropin alfa - Fertinex®] is higher than – 1fertilized oocyte. The second objective looking for the non-inferiority of the revised formulation of follitropin alfa vs. Gonal-f®, non-inferiority y will be declared if the lower limit of 95% CI difference between the revised formulation of follitropin alfa and Gonal-f® is higher than – 1fertilized oocyte.

Study 21884 was a prospective, randomized, assessor-blind, multi-national, multi-center (34 centers throughout the United States and Argentina), comparative study that recruited infertile women undergoing assisted reproductive technology procedures [either patients undergoing *in vitro* fertilization (IVF) or patients undergoing *in vitro* fertilization with intra-cytoplasmic injection (IVF/ICSI)]. The enrollment criteria were appropriate. All patients received down-regulation using a gonadotropin releasing hormone agonist (Lupron®). Subjects ready to begin treatment (after appropriate down-regulation measured by ultrasound and estradiol criteria) were

randomized in a 1:1:1 ratio to receive the revised formulation of follitropin alfa, Gonal-f® or Fertinex®. The method of insemination (conventional IVF or ICSI) was to be selected at the time of randomization prior to treatment initiation. Randomization was stratified by center, age (up to 34 years old and 35 years old and greater) and method of insemination (in vitro fertilization [IVF] or intracytoplasmic injection [ICSI]). In the NDA submission, the Sponsor presented a per protocol analysis using a two-sided 90% confidence interval (C.I.) [See Table 3 (to follow) from Statistical Reviewer's Table 3.3].

Table 3. Sponsor's Analysis, Per Protocol Population, of Fertilized Oocytes from Study 21884[a]

	Fertinex® (N=218)	revised formulation of follitropin alfa (N=216)
Number of Fertilized Oocytes		
Mean (s.d.)	6.0 (3.7)	6.7 (4.1)
Median (min, max)	5 (0, 18)	6 (0, 22)
Treatment Difference of the Mean (two-sided 90% C.I.)[b]		0.74 (0.11, 1.36)

[a]Source: Statistical reviewer Table 3.3, Sponsor Tables 31 and 33 Study 21884 report.
[b]Treatment difference revised formulation of follitropin alfa and Fertinex® using 2-sided 90% confidence interval based on 4-way ANOVA with effects for treatment (revised formulation of follitropin alfa, approved Gonal-f® and Fertinex®) center, age and method of insemination strata.

The final amended protocol, dated August 09, 2000, called for use of an intent-to-treat analysis (ITT) analysis using a 95% C.I. Therefore, the Statistical reviewer performed the review as called for in the final amended protocol, an ITT analysis with a (2-sided) 95% C.I. With the revised final protocol, Serono states, that along with the comparison of the revised formulation of follitropin alfa to Fertinex, the comparison between the revised formulation of follitropin alfa to Gonal-f® is related to the primary objective of the bioequivalence study which aims to compare the bioavialabiity and confirm the bioequivalence between the revised formulation and Gonal-f®. Therefore, even though the Sponsor only presents the analyses comparing the revised formulation of follitropin alfa to Fertinex®, this reviewer will also look at the results compared to Gonal-f®. The ITT analysis is presented in Table 4.

Table 4. Division's Analysis, ITT Population, of Fertilized Oocytes from Study 21884[a]

	Fertinex® N=237	revised formulation of follitropin alfa N = 237	Gonal-f® N=237
Number of Fertilized Oocytes			
Mean (s.d.)	5.9 (3.9)	6.3 (4.3)	5.9 (4.3)
Median (min, max)	5 (0, 18)	6 (0, 22)	5 (0, 24)
Treatment Difference of the Median (two-sided 95% C.I.)[b]		1 (0, 1)	
Treatment Difference of the Median (two-sided 95% C.I.)[c]		0 (0, 1)	

[a]Source: Statistical reviewer Table 3.4 (prepared from SAS data sets provided by the Sponsor, Medical Officer Table 7A

[b]Median treatment difference revised formulation of follitropin alfa and Fertinex® using 2-sided 95% confidence intervals based on the Hodges-Lehmann estimate (for non-normally distributed data) for the treatment difference.

[c] Median treatment difference revised formulation of follitropin alfa and Gonal-f® using 2-sided 95% confidence interval based on the Hodges-Lehmann estimate (for non-normally distributed data) for the treatment difference.

As stated previously, the final amended protocol also provided that all subjects receive either conventional IVF or ICSI as their method of insemination and that the particular method was to be selected at the time of randomization prior to treatment initiation. Further, randomization was to be stratified by the method of insemination. This amendment change was in response to the Division's strong recommendation that if fertilized oocytes were used at the primary outcome variable, then only conventional IVF should be performed and not ICSI. This recommendation was based on the literature support that for certain infertility diagnosis (example severe male factor) ICSI yields superior fertilization rates compared to conventional IVF. Serono ignored the Division's recommendation citing instead that the company strongly believes that fertilization rates obtained with IVF and ICSI were comparable and that the ICSI procedure would not bias results. The Division agrees that for couples who are likely to have normally high fertilization rates with conventional IVF (i.e. tubal factor), ICSI is unlikely to make a difference in fertilization outcomes and is thus, for these groups, an unnecessary procedure. However, the use of ICSI in couples with severe male factor, previous fertilization failures, or possibly unexplained infertility, if it were applied preferentially in one treatment group vs. the other would offer a significant treatment advantage to that group. Therefore, the reviewers were asked to look at the subgroup data based on insemination method, conventional IVF vs. ICSI. A total of 64 subjects had randomization errors related to the method of insemination. Table 5 presents subgroup analyses based on the method of insemination.

Table 5. Division's Sub-Group Analysis Based on Method of Insemination for Fertilized Oocytes from Study 21884[a]

	Fertinex®	revised formulation of follitropin alfa	Gonal-f®
Subgroup ITT (all subjects treated and assigned to actual insemination method)			
IVF Subjects			
n	92	88	101
mean (s.d.)	5.8 (4.1)	6.1 (4.4)	5.8 (4.3)
median (min, max)	5 (0, 18)	6 (0, 20)	5 (0, 24)
Treatment Difference of the Median (two-sided 95% C.I.)[b]		0 (-1, 2)	
Treatment Difference of the Median (two-sided 95% C.I.)[c]		0 (-1, 1)	
ICSI Subjects			
n	134	140	136
mean (s.d.)	5.8 (3.5)	6.5 (4.3)	6 (4.3)
median (min, max)	5 (0, 17)	6 (0, 22)	5 (0, 20)
Treatment Difference of the Median (two-sided 95% C.I.)[b]	1 (0, 1)	1 (0, 1)	
Treatment Difference of the Median (two-sided 95% C.I.)[c]		1 (0, 2)	
Per protocol Population[d]			
IVF Subjects			
n	87	88	89
mean (s.d.)	5.9 (4.2)	6.1 (4.4)	5.8 (4.5)
median (min, max)	5 (0, 18)	6 (0, 20)	5 (0, 24)
Treatment Difference of the Median (two-sided 95% C.I.)[b]		0 (-1, 1)	
Treatment Difference of the Median (two-sided 95% C.I.)[c]		0 (-1, 2)	
ICSI Subjects			
n	127	132	124
mean (s.d.)	5.8 (3.6)	6.5 (4.2)	5.9 (4.3)
median (min, max)	5 (0, 17)	6 (0, 22)	5 (0, 20)
Treatment Difference of the Median (two-sided 95% C.I.)[b]		1 (0, 1)	
Treatment Difference of the Median (two-sided 95% C.I.)[c]		1 (0, 2)	

[a] Source: Prepared by Statistical Reviewer from SAS data sets submitted by the Sponsor.
[b]Median treatment difference revised formulation of follitropin alfa and Fertinex® using 2-sided 95% confidence intervals based on the Hodges-Lehmann estimate for the treatment difference.
[c] Median treatment difference revised formulation of follitropin alfa and Gonal-f® using 2-sided 95% confidence interval based on the Hodges-Lehmann estimate for the treatment difference.
[d] Per protocol excludes the following 66 subjects: 2 who were not treated with FSH, 33 who changed insemination procedure (IVF to ICSI or ICSI to IVF), 2 who had IUI and 29 who had mixed inseminations.

Even thought these studies were not powered for sub-group analyses this reviewer believes that some observations are notable. It is unclear why the numbers of subjects randomized to receive ICSI should have been conspicuously different than those randomized to receive conventional IVF for each drug treatment group (140 -ICSI vs. 88-IVF for the revised formulation of follitropin alfa group and 134-ICSI vs. 92-IVF for the Fertinex group). The impact of this on the study is unknown, but because of the larger population of ICSI subjects, the study results were apparently driven by ICSI. However, it did not appear that the randomization violations to ICSI in the revised formulation of follitropin alfa group were selectively enriched with the populations expected to receive the most benefit from ICSI. Both the analysis looking at the ITT population and the per protocol (excluding all randomization violations) showed non-inferiority of the revised formulation of follitropin alfa to Fertinex® for subjects receiving ICSI but a marginal or borderline efficacy (with respect to non-inferiority of the revised formulation of follitropin-alfa to Fertinex®) for subjects receiving conventional IVF.

Issues related to sub-group analyses based on age and treated subjects in the United States vs. subject treated in Argentina are all discussed in the primary Medical Officer's review and do not substantially affect the outcome and recommendation for this application.

The clinical pregnancy rate was a secondary variable. Clinical pregnancy in this study was defined by the presence of a fetal sac with or without a fetal heartbeat. There was a clinical pregnancy rate of 29.8% in the revised formulation of follitropin alfa vs. a clinical pregnancy rate of 35% in Fertinex and 35% in Gonal-f. The twin birth rate was 22.9% and the triplet rate was 5.7% in the revised formulation of follitropin alfa group. The rates of multiple gestation were not higher than the comparators.

Safety

The rate of adverse events across all treatment arms were similar (60.3% in Fertinex®, 61.2%-revised formulation of follitropin alfa and 64.6% in Gonal-f®. The most commonly reported adverse events were headache and abdominal pain.

There were no deaths in Study 21884. In the revised formulation of follitropin alfa there were 3 ectopic pregnancies, 1 fetal death, 1 missed abortion and 1 case of fetal Down's syndrome as well as 1 fetal acrania. In addition, there was 1 case of ovarian hyperstimulation syndrome. The overall pregnancy-related adverse events and the rate of ovarian hyperstimulation syndrome, as well as other serious adverse events, were similar across all treatment groups and no obvious safety concerns were noted in the Medical Officer' safety review.

Division of Scientific Investigations (DSI)

DSI audits for Studies 21884 and 22240 were completed between September and November 2003, and no problems were noted in the DSI inspections performed. The final DSI report dated January 16, 2004, recommended that all clinical sites be accepted in support of the application for revised formulation of follitropin alfa.

Chemistry/Manufacturing

The following summary addresses the major issues identified in the chemistry review.

The drug substance, follitropin alfa, is a recombinant version of the human follicle-stimulating hormone (FSH) genetically engineered from Chinese Hamster Ovary Cells and it was previously approved in NDA 20-378. Since the approval of the NDA, there have been no significant manufacturing changes in the currently approved drug substance manufacturing process.

The drug product, Tradename (follitropin alfa for injection), is a new formulation for the currently approved Gonal-f® (NDA 20-378). Tradename is supplied in the form of sterile, lyophilized powder for injection in single-dose vials filled with 41 IU (3 µg), 82 IU (6 µg), or 165 IU (12 µg) to deliver 37.5 IU (2.8 µg), 75 IU (5.5 µg), or 150 IU (11 µg) of follitropin alfa, respectively. Each vial of Tradename also contains 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, and 0.05 mg polysorbate 20. O-phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment.

The formulation for Tradename (follitropin alfa for injection) differs from that for Gonal-f® (follitropin alfa for injection) in the addition of two inactive ingredients: methionine —— , and polysorbate 20 ——. The amount of the oxidized α-subunits in Tradename, containing methionine and polysorbate 20, appears to increase minimally after long-term storage. Available stability data for Tradename support an expiry of 24 months when stored at 25±2 °C.

Tradename single-dose vials are available in six different configuration of packages containing one or ten vials of follitropin alfa for injection (37.5 IU, 75 IU, or 150 IU), one or ten pre-filled syringes containing the diluent (Sterile Water for Injection, USP), one 18-gauge reconstitution needle, and one 27-gauge administration needle.

Three manufacturing sites —— were proposed for the revised formulation of follitropin alfa for injection. These sites are all previously approved. The Office of New Drug Chemistry (ONDC) was asked to decide whether inspections would be requested for these manufacturing sites. ONDC decided (see Chemistry review) that because these sites are approved and the manufacturing process is essentially the same as the old formulation, no inspection request would be made.

NDA 21-765 is recommended for Approval from the standpoint of Chemistry, Manufacturing and Controls.

Product Name

A change in the tradename from Gonal-F® (capital F) to Gonal-f® (lower case f) for the original formulation was reviewed by DMETS on 21-Jan-03, and found to be acceptable. The Tradename

request for the revised formulation of follitropin alfa was received from the Sponsor on March 15, 2004. This tradename [redacted], is under review by DMETS.

APPEARS THIS WAY
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APPEARS THIS WAY
ON ORIGINAL

Pre-clinical Pharmacology and Toxicology

This application is for a new formulation for follitropin alpha for injection. It differs from the original GONAL-f® formulation in the addition of two inactive ingredients: methionine [redacted], and polysorbate 20 [redacted]. Both inactive ingredients have a prior history of use in drug products and are deemed safe. From a Pharmacology/Toxicology viewpoint, NDA 21-765 is recommended for Approval

Clinical Pharmacology and Biopharmaceutics

No studies related to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) were submitted in this application. OCPB has only labeling recommendations. The Sponsor was requested to [redacted]

Discussion, Conclusions and Labeling Recommendations

This reviewer concurs with the Medical Officer and Statistical review that efficacy (in the form of non-inferiority to Gonal-f® on the primary endpoint of rate of ovulation in Study 22240) has been established for the revised formulation of follitropin alfa for the indication of induction of ovulation and pregnancy in oligo-anovulatory infertile patient in whom the cause of infertility is functional and is not due to primary ovarian failure. However, because the population of oligo-anovulatory patients was different (based on the enrollment criteria), one may not be able to make directs comparisons of the ovulation rate and pregnancy rates between this trial and that of previous gonadotropins for this indication. Specifically the requirement for clomiphene-resistance was dropped and women with insulin resistance and women on insulin-sensitizing agents were allowed into Study 22240 supporting ovulation induction for this NDA. If approved, labeling should clearly indicate the population of oligo-anovulatory women used in the study of the revised formulation of follitropin alfa.

This reviewer also concurs, with some reservations, that efficacy (in the form of non-inferiority to Fertinex® on the primary endpoint of fertilized oocytes in Study 21884) has been established for the revised formulation of follitropin alfa for the indication of development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program. While overall non-inferiority of the revised formulation of follitropin alfa to Fertinex® was demonstrated, the subgroup analysis for conventional IVF was marginal indicating that the overall results were driven by the ICSI group (sub-group analysis of which unambiguously met the criterion for non-inferiority). ICSI is known to have superior fertilization results for certain infertility diagnoses such as severe male factor. The Division made a recommendation to the Sponsor not to include ICSI as the method of insemination in the same study looking at conventional IVF. This recommendation was not followed. The two insemination methods for ART are recognized as different. This was acknowledged by the Advisory Committee for Reproductive Health in its September 2003 meeting addressing the issue of trials for gonadotropin products. The Advisory Committee felt the analyses for gonadotropins in ART should, at least, be stratified by method of insemination (as was done in Study 21884). If the NDA is approved for the revised formulation of follitropin alfa, the label should provide some subgroup information with the notation that Study 21884 was not powered to demonstrate differences in subgroups. The Sponsor has agreed to all labeling recommendations from the Division.

I concur with the recommendations from all review disciplines that NDA 21-765 be Approved. This reviewer recommends against the tradename, [redacted].

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

cc: Division File NDA 21-684
D. Shames, MD
A. Gassman, MD
S. Al-Habet, Ph.D.
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/s/

Shelley Slaughter
3/25/04 02:22:21 PM
MEDICAL OFFICER

Tradename

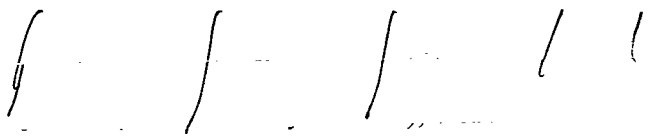
NDA 21-765 (originally 20-378/Serial No. 032)

Medical Officer's Review
NDA 21-765/(Serial Number 000)
(Originally 20-378/SE8-032)

Date NDA Submitted: April 29, 2003
Date NDA Received: May 28, 2003
Review Completed: March 24, 2004

Medical Officer's Review
(Original Review)

Sponsor:	Serono, Inc. One Technology Place Rockland, MA 02370
Drug name:	
Generic:	follitropin alfa for injection
Trade:	Tradename
Chemical:	recombinant human follicle stimulating hormone (r-hFSH)
Pharmacologic category:	Gonadotropins
Proposed indications:	Women: 1) Tradename is indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure. 2) Tradename is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology program.
Dosage Form and Route of Administration:	Lyophilized powder in vials for reconstitution for subcutaneous administration
Active ingredient:	Recombinant human follicle stimulating hormone (r-hFSH)
Strength:	Each r-hFSH Single Dose vial is filled with r-hFSH in a lyophilized powder to deliver 37.5 IU (2.8 μg), 75 IU (5.5 μg), or 150 IU (11 μg) of r-hFSH, respectively. Single dose vials are reconstituted with Sterile Water for Injection, USP.



Dosage:	The dose of Gonal-f® to stimulate development of the follicle must be individualized for each patient. Doses may range up to 300 IU/day depending on the individual patient response.

Dosage (continued):

Infertile patients with oligo-anovulation: The initial dose of the first cycle be 75 IU of Tradename per day, administered subcutaneously An incremental adjustment in dose of up to 37.5 IU may be considered after 14 days. Further dose increases of the same magnitude could be made, if necessary, every seven days. Treatment duration should not exceed 35 days unless an E2 rise indicates imminent follicular development.

Assisted Reproductive Technologies patients: Therapy with Tradename should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 IU per day, until sufficient follicular development is attained. In most cases, therapy should not exceed ten days. In patients undergoing ART under 35 years old, whose endogenous gonadotropin levels are suppressed, Tradename should be initiated at a dose of 150 IU per day. In patients 35 years old and older whose endogenous gonadotropin levels are suppressed, Tradename should be initiated at a dose of 225 IU per day. Treatment should be continued until adequate follicular development is indicated as determined by ultrasound in combination with measurement of serum estradiol levels. Adjustments to dose may be considered after five days based on the patient's response; subsequently dosage should be adjusted no more frequently than every 3-5 days and by no more than 75-150 IU additionally at each adjustment.

Related Submissions:

IND 38,712 (Currently approved Gonal-f® in a lyophilized powder)
NDA 2-378 (Currently approved Gonal-f® in a lyophilized powder)
NDA 21-684 (Gonal-f® Pen contains a liquid formulation of Gonal-f® in an injector-pen device)

Related documents reviewed:
Approved Gonal-f® product:

- Original NDA submission for the approved Gonal-f® product (20-378) was 15-Sep-93.
- Original Medical Officer's review of the current approved Gonal-f® product was 03-Mar-94.
- Three summaries of Medical Officer's Reviews of Amendments for Gonal-f® product (NDA 20-378) were dated: 18-Apr-96, 26-Nov-96, and 13-Feb-97.
- Medical Officer's Review of Safety Update for the approved Gonal-f® product (NDA 20-378) was dated 17-Jul-97.
- Original Approvable Action letter for the approved Gonal-f® product (NDA 20-378) was dated 29-Sep-97.

Related documents reviewed:
Approved Gonal-f® product (continued):

- Annual Report to IND 38,712 for the approved Gonal-f® product for the period 2001-2002 (NDA 20-378/ Serial No. 105-YY) was dated 28 Mar 2002.
- Periodic Annual Report for the currently approved Gonal-f® formulation (submitted to NDA 20-378/ P-015) was dated 25-Nov-03) for the time period from 23 Sep 2002 through 22 Sep 2003.

Related documents for the New r-hFSH formulation: (NDA 20-378/Serial No. 015 and 016)

- Original briefing document for the new Gonal-f® formulation (r-hFSH) to IND 38,712 for meeting to discuss the new r-hFSH formulation change was submitted 23-Dec-99.
- Meeting Minutes were dated 06-Jan-00 (Internal meeting – Chemistry).
- Meeting Minutes were dated 13-Jan-00 (Guidance meeting with sponsor – Chemistry).
- Meeting Minutes were dated 14-Jan-00 (Guidance meeting with sponsor – Clinical).

Studies 21859 and 22596 (Bioequivalence):

- Original protocol for bioequivalence study 21859 submitted to IND 38,712 (PN-082) was dated 13-Mar-00.
- Completed bioequivalence studies (IMP 21859 and IMP 22596) were submitted 03-Aug-01.
- Clinical Pharmacology and Biopharmaceutics Review was dated 30-Nov-01.
- Agency's Approvable letter for NDA 20-378/S016 was dated 21-Dec-01.
- Agency's Approvable letter for NDA-20-378/SCF-015 was dated on 28-Feb-02.
- Teleconference with sponsor to discuss bioequivalence studies IMP 21859 and IMP 22596 submitted in SCF-015 and SCF-016) was held on 11-Dec-02.
- Advice letter to sponsor on lack of bioequivalence in studies 21859 and 22596 was dated 26-Mar-03.

Study 21884 (In Vitro Fertilization [IVF]):

- Original protocol for study 21884 submitted to IND 38,712 (PN-083) was dated 20-Mar-00,
- Statistical Analysis Plan for study 21884 submitted to IND 38,712 (PN-081) was dated 13-Mar-00.
- Statistician's Review of the protocol and statistical plan for study 21884 (PN-081 and 083) was dated 15-May-00.
- Medical Officer's Review of Request for Special Protocol Review of the protocol for study 21884 was dated 18-May-00.
- Division's letter to sponsor re: protocol for study 21884 submitted to IND 38,712 (PN-081,-082 and -083) was dated 31-May-00.
- Protocol Amendment One for study 21884 containing the final protocol for study 21884 was dated 10-Aug-00.
- Completed study 21884 was submitted to NDA 20-378 (Serial No. 032) on 27-May-03

Study 22240 (Ovulation Induction [OI]):

- Original protocol for study 22240 submitted to IND 38,712 (PN-094) dated 20-Feb-01.
- Completed study 22240 was submitted to NDA 20-378 (Serial No. 032) on 27-May-03.

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Clinical Review for NDA 20-378

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approval of the application for the new formulation of Gonal-f® (Tradename) is recommended from a clinical perspective. The decision for the recommendation of an approvable action is based on the sponsor's demonstration of clinical non-inferiority of the new filled by mass (designated as r-hFSH) Gonal-f® formulation in two separate clinical studies to approved gonadotropin products.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

In addition, the applicant should continue to submit post-marketing experience obtained from all countries where the new formulation of the drug is marketed.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The approved Gonal-f® is a preparation of the human gonadotropin follicle stimulating hormone (FSH) produced by genetic engineering in Chinese Hamster Ovary (CHO) cells. The FSH protein is then purified by a process that results in a lyophilized powder with the specific activity of FSH *in vivo* when injected. Gonal-f® was approved for the treatment of female infertility on 29 Sep 1997.

The original NDA for Gonal-f® was submitted 15 Sep 1993. The basis of the NDA was evaluating whether Gonal-f® was as effective and safe in treating female infertility patients as a reference urinary drug product. Approval of the NDA 20-378 was recommended on 03 Mar 1994 by the reviewing Medical Officer based on one adequate well controlled comparative phase III clinical study (GF 5503). The recommendation for approval was also based on two other completed clinical pharmacology studies and 19 ongoing studies.

Significant deficiencies in manufacturing and quality control of Gonal-f® resulted in a "Not Approvable" letter issued on 13 Sep 1994. The sponsor submitted several amendments including one on 15 Jan 1997 that responded to all deficiencies. However, in the Jan 1997 Amendment the sponsor had added a new "Clinical Studies" section to the labeling that included data from three clinical studies that were ongoing at the time of the original NDA review and had not been reviewed in detail.

The sponsor submitted an additional amendment on 10 Jul 1997 that incorporated (by cross-reference to IND 38,712) the final study reports of the three clinical studies mentioned in the label. The Division reviewed the three clinical studies and labeling information. The Division concluded that the sponsor had satisfactorily addressed all deficiencies after submission of a safety update (17 Jul 1997). Gonal-f® was approved in an Action Letter dated 29 Sep 1997. The Division concluded that the completed clinical studies demonstrated that Gonal-f® was as effective and safe as the marketed urinary hFSH preparations for follicular development and ovulation induction.

In December 1999, the sponsor proposed a new Gonal-f® formulation that would be filled-by-mass instead of being filled using bioactivity. The sponsor stated that the new Gonal-f® formulation would improve batch-to-batch variability.

The sponsor met with the Division on January 13th and 14th, 2000 to discussion chemistry and clinical issues required for approval of the new Gonal-f® formulation. The sponsor was advised that:

1. / / / /
2. Approval of the new Gonal-f® formulation would require bioequivalence studies.

Two completed bioequivalence studies (IMP 21859 and 22596) were submitted for approval of the new Gonal-f® formulation on 03 Aug 2001. An additional submission for inclusion of a new dosage strength, Gonal-f® Multi-dose 450 IU (S-016) was submitted on 22 Aug 2001.

Two pharmacokinetic studies (studies IMP 21859 and IMP 22596) were submitted to demonstrate bioequivalence of the proposed doses of new lyophilized powder formulation (S-015 and 016) to the currently approved Gonal-f® product.

The Biopharmacologist's review (dated 11 Dec 2001) concluded that the new formulation (r-hFSH) was not bioequivalent to the currently approved Gonal-f® lyophilized powder formulation.

Approvable letters for the two supplements (S015 and S016) for new r-hFSH formulation (dated 21 Dec 2001 and 28 Feb 2002) were sent to the sponsor, but the Biopharmacologist's comments were inadvertently not relayed to the sponsor. The sponsor was subsequently informed at a preNDA teleconference on 11 Dec 2002 of the Division's conclusion that the new r-hFSH formulation (fill-by-mass) was not bio-equivalent to the currently marketed Gonal-f® formulation (fill-by-biological activity). The lack of bio-equivalence of the two formulations was briefly discussed at the December 2002 teleconference. 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. The sponsor stated during the May meeting that there was no current explanation for the lack of bio-equivalence between the proposed and the currently approved formulation. At the May meeting, the sponsor proposed submission of two completed clinical studies (studies 21884 and 22240) to demonstrate efficacy and safety of the new r-hFSH formulation (vials filled by mass). These two clinical studies (studies 21884 and 22240) would use clinical endpoints to demonstrate that the new r-hFSH was non-inferior to currently approved FSH products for each of the female indications (ovulation induction and use in patients undergoing Assisted Reproductive Technology procedures). The Division agreed to evaluate the two phase III clinical studies. Studies 21884 and 22240 were submitted electronically on 27 May 2003.

A tradename request for the new formulation of r-hFSH was received from the sponsor on 15-Mar-04. This tradename is under review by DMETS.

B. Efficacy

Efficacy of the currently approved Gonal-f® formulation was previously established in four comparative clinical studies (see NDA 20-378). These clinical studies compared the currently approved Gonal-f® formulation to urinary menotropins using clinical endpoints. The sponsor proposed that the new formulation of Gonal-f® (r-hFSH) be approved for the same indications in women as the currently marketed Gonal-f® formulation for the following reasons:

1. The manufacturing process for the new r-hFSH formulation performs the filling of vials based on weight rather than biologic activity. The sponsor states that this change in the filling of vials is not anticipated to affect the basic physiochemical, immunologic and biologic properties of the r-hFSH formulation *in vivo*.

Efficacy (continued):

2. The sponsor believes that non-inferiority of the new r-hFSH formulation in women was demonstrated to an approved reference product (Fertinex® or the approved Gonal-f® formulation) in two clinical studies (studies 21884 and 22240), one study for each indication in women.

Study 21884 was submitted for the first proposed indication, for infertile women in an assisted reproductive technology program. Study 22240 was submitted for the second proposed indication, for ovulation induction in anovulatory infertile women. Statistical analysis of the new r-hFSH formulation used in studies 21884 and 22240 demonstrated non-inferiority to an approved FSH gonadotropin product (Fertinex® for study 21884 and Gonal-F® for study 22240) using pre-specified clinical endpoints (ovulation rate as demonstrated by serum progesterone levels and mean number of fertilized oocytes). The lack of bioequivalence in the two pharmacokinetic studies (studies IMP 21859 and IMP 22596) does not appear to translate into clinically significant differences when comparing overall use of the new r-hFSH formulation to the approved Gonal-f® or Fertinex® for the proposed indications in women.

The proposed indications for the new Gonal-f® (r-hFSH) formulation in women are identical to the labeling for the approved Gonal-f® product: ovulation induction in oligo-anovulatory women and for follicular development in women who are undergoing assisted reproductive technology.

C. Safety

Clinical safety data contained in NDA 20-378 and pertinent annual reports provide the current safety profile for the approved formulation of Gonal-f®. The safety profile for the new fill-by-mass formulation of Gonal-f® (r-hFSH) was obtained from the two submitted clinical studies (21884 and 22240). The safety data demonstrated that the safety profile for the new r-hFSH formulation was similar to both the currently marketed Gonal-f® formulation and to a urinary follicle stimulating hormone product (Fertinex®).

D. Dosing

3 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

E. Special Populations

The sponsor is seeking approval for this r-hFSH drug product for conditions that occur in infertile women. The studied indications for gonadotropin treatment for the new r-hFSH formulation are for controlled ovarian hyperstimulation and ovulation induction. These indications do not apply to pediatric or geriatric populations. This drug is contraindicated in pregnancy.

The sponsor has not chosen to study this new r-hFSH formulation for the male indication of induction of spermatogenesis in hypogonadotropic hypogonadal men.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: follitropin alfa for injection

Proposed Trade Name: Tradename
Drug Class: Gonadotropins

Proposed indications: Women:

1) Tradename is indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

2) Tradename is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology program.

Dosage Form and Route of Administration: Lyophilized powder in vials for reconstitution for subcutaneous administration

Strength: Each r-hFSH Single Dose vial is filled with r-hFSH in a lyophilized powder to deliver 37.5 IU, 75 IU, or 150 IU of r-hFSH, respectively. Single dose vials are reconstituted with Sterile Water for Injection, USP. (**NDA 20-378/S-015**)

Dosage: The dose of Gonal-f® to stimulate development of the follicle must be individualized for each patient. Doses may range up to 300 IU/day depending on the individual patient response.

Dosage (continued):

Infertile patients with oligo-anovulation: The initial dose of the first cycle be 75 IU of Tradename per day, administered subcutaneously An incremental adjustment in dose of up to 37.5 IU may be considered after 14 days. Further dose increases of the same magnitude could be made, if necessary, every seven days. Treatment duration should not exceed 35 days unless an E2 rise indicates imminent follicular development.

Assisted Reproductive Technologies patients: Therapy with Tradename should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 IU per day, until sufficient follicular development is attained. In most cases, therapy should not exceed ten days. In patients undergoing ART under 35 years old, whose endogenous gonadotropin levels are suppressed, Tradename should be initiated at a dose of 150 IU per day. In patients 35 years old and older whose endogenous gonadotropin levels are suppressed, Tradename should be initiated at a dose of 225 IU per day. Treatment should be continued until adequate follicular development is indicated as determined by ultrasound in combination with measurement of serum estradiol levels. Adjustments to dose may be considered after five days based on the patient's response; subsequently dosage should be adjusted no more frequently than every 3-5 days and by no more than 75-150 IU additionally at each adjustment.

B. State of Armamentarium for Indication(s)

There are many gonadotropin products, including urinary and recombinant derived human follicle stimulating hormone (FSH) products that are currently marketed in the United States. These FSH preparations are used for controlled ovarian hyperstimulation and ovulation induction in infertile women. Gonal-f® is one of two recombinant FSH products available in the U.S.

The new formulation of Gonal-f® (r-hFSH) uses the same recombinant derived h-FSH as the approved product Gonal-f®, but has some significant chemistry and manufacturing changes. The new formulation is:

- Filled-by-mass (weight) instead of filled using biologic activity (IU).
- Contains — -methionine) and — (Tween 20) —

The Division met with the Sponsor on 13-Jan-00 and agreed that the chemistry and manufacturing changes were considered a major post-approval change and would require a new supplemental NDA with necessary Chemistry, Manufacturing, and Control information as well as a new bioequivalence study to be conducted comparing the new r-hFSH with the current Gonal-f®, formulation.

C. Important Milestones in Product Development

Improvements in purification resulted in separating follicle stimulating hormone (FSH) from other proteins in human menopausal urine. Purified FSH was first introduced in 1982. In the 1990's Chinese Hamster Ovary (CHO) cells were developed that are capable of producing biologically active FSH in culture. Recombinant derived FSH is from *in vitro* cultured cells and is not clinically different from native human FSH. The approved Gonal-f® product was quantified using a specific activity of FSH per milligram of protein. The sponsor states that the proposed change in chemistry and manufacturing of Gonal-f® (filled-by-mass) will increase consistency between vials.

The Division initially approved the supplemental NDA for the new r-hFSH formulation changes. This formulation change was initially Approvable. (See Approval letters dated 21 Dec 2001 and 28 Feb 2002). Inadvertantly, the Biopharmacology Review stating the r-hFSH formulation was not bioequivalent to the approved Gonal-f® formulation had not been incorporated into the Division's response letter to supplements 015 and 016. A follow-up letter was sent to the sponsor on 26-Mar-03 informing the sponsor of the lack of bioequivalence and that the NDA supplements 015 and 016 were not approvable.

The Division discussed alternatives for approving the fill-by-mass Gonal-f® formulation (r-hFSH) with the sponsor at the May 2003 meeting. At that May meeting, the sponsor proposed submission of two completed clinical studies (studies 21884 and 22240) to demonstrate clinical non-inferiority of the new r-hFSH formulation. The Division agreed at the May 2003 meeting to review the two clinical studies. The completed clinical studies (21884 and 22240) were submitted on 27-May-03.

E. Other Relevant Information

The sponsor submitted an additional proposal for a liquid Gonal-f® formulation. An additional bioequivalence study comparing the Gonal-f® liquid formulation to the Gonal-f® fill-by-mass formulation (S-015) was initially discussed with the Division in a teleconference on December 2002. In a May 2003 meeting, the Division stated that the outcome of the liquid formulation application (S-016) would be depend on the outcome of the fill-by-mass application (S-015).

Other Relevant Information (continued):

In addition, the sponsor has proposed a pen injector device that will be used for subcutaneous injection of the proposed liquid Gonal-f® formulation.

The sponsor also requested changing the original trademarked name of Gonal-F® (capital letter F) to Gonal-f® (lower case f). This trademark change was reviewed by DMETS and accepted on 21-Jan-03. The sponsor proposed to differentiate the new liquid formulation in a disposable device by having a suffix such as "Pen", ——— after the proprietary name. These new suffixes will be reviewed concurrently by DMETS when the liquid Gonal-f® formulation amendment is submitted.

E. Important Issues with Pharmacologically Related Agents

The therapeutic properties and use of human gonadotropins in women has been well documented in the published literature. The original clinical trial data for the approved Gonal-F® drug product demonstrated non-inferior efficacy to a referenced approved urinary-derived drug product. Furthermore, the dynamics of follicular growth and ovulation with use of the approved formulation of Gonal-f® have been well characterized.

The two treatment modalities (ART and ovulation induction) produce multiple key clinical variables that can be evaluated including fertilization rate, ovulation rate and clinical pregnancy rate. The pre-specified primary efficacy variables generated by these two studies were used to establish clinical non-inferiority of the new r-hFSH formulation by direct comparison of treatment arms to other approved gonadotropin products.

The most significant hazard of gonadotropin therapy is ovarian hyperstimulation syndrome. For r-hFSH, the ovarian hyperstimulation syndrome rate is of special concern because of the lack of bioequivalence seen in the pharmacokinetic studies. The overall rate for significant ovarian hyperstimulation syndrome can range up to 5%, with a severe ovarian hyperstimulation rates from 0.1–2% for patients using assisted reproductive technology.[1,2]

A second, although less common serious adverse event observed with gonadotropin therapy is thromboembolism. Thromboembolism may present with or without ovarian hyperstimulation, and is usually seen in less than 1% of patients with moderate and severe ovarian hyperstimulation. The mechanism for development of thromboembolism may occur in the presence of high serum estradiol levels pre-and post-gonadotropin treatment.

Important Issues with Pharmacologically Related Agents (continued):

The most current worldwide experience (2002-2003) with the current approved Gonal-f® formulation reveals only two reported thromboembolic events (both cases were associated with ovarian hyperstimulation syndrome) and one reported case of a pulmonary embolism (See periodic safety report in NDA 20-378/Serial No. P-015).

Reviewer's comment: In the opinion of this reviewer, similarity of the new r-hFSH formulation to approved gonadotropin formulations is also supported through documentation of similar clinical safety profiles.

F. Foreign Approvals of new Gonal-f® formulation:

There is no indication that the approved Gonal-f® formulation has been withdrawn from the overseas market for any reason. The sponsor has not reported any actions for safety reasons that were initiated by any regulatory authority or by the sponsor on the approved Gonal-f® to date.

G. Other Pharmacologically Related Agents Under Study:

The sponsor has proposed a liquid formulation of Gonal-f® that was submitted in a pre-sNDA package submitted on 12-Nov-02 and discussed at a teleconference on 11-Dec-02. The sponsor also plans to use the new liquid formulation in a —— ——, with the new liquid formulation of Gonal-f® will be part of a subcutaneous injector-pen device for subcutaneous injection of gonadotropin therapy.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please refer to the pharmacologist's, chemist's and microbiologist's reviews for the pertinent findings. No additional pending approvability issues for CMC, Toxicology, Biopharmaceutics, or Microbiology issues are noted for the new r-hFSH formulation.

In addition, a change in the tradename from Gonal-F® (capital F) to Gonal-f® (lower case f) was reviewed by DMETS on 21-Jan-03, and found to be acceptable.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics/Pharmacodynamics

The currently approved formulation of Gonal-f® has similar chemical and biological properties to native human follicle stimulating hormone (hFSH). The sponsor submitted bioequivalence studies for the new fill-by-mass formulation of Gonal-f® (r-hFSH) to the currently approved Gonal-f® formulation. The Office of Clinical Pharmacology and Biopharmaceutics reviewed the bioequivalence studies (study IMP 21859 and study IMP 22596) submitted in SCF-015 and SCF-016. The conclusion of the Biopharmaceutical reviewer (original review date 11-Dec-01) was that the analysis had demonstrated that the two products (the current Gonal-f® formulation and the fill-by-mass formulation of Gonal-f® (r-hFSH) failed to show bioequivalence.

The sponsor indicated at the May 2003 meeting that there was no current explanation for the lack of bioequivalence between the two formulations. As a result of the meeting on May 2003, the Division agreed to evaluate the two completed clinical studies (studies 21884 and 22240) for the purposes of establishing non-inferiority of the new r-hFSH formulation to approved r-FSH products.

IV. Description of Clinical Data and Sources

A. Overall Data

Previous clinical information:

Four comparative clinical trials (NDA 20-378) were originally submitted to demonstrate efficacy and safety for the current approved formulation of Gonal-f®. These clinical trials for approved Gonal-f® were reviewed in detail (See previous Medical Officer's Review of 03 Mar 1994, three summaries of Medical Officer's Reviews of Amendments for Gonal-f® product (NDA 20-378) dated: 18-Apr-96, 26-Nov-96, and 13-Feb-97 and Medical Officer's Review of Safety Update for the approved Gonal-f® product (NDA 20-378) dated 17-Jul-97.)

Since the approval of the current Gonal-f® formulation in 1997, the efficacy and safety data for the current approved Gonal-f® formulation has been updated in both published literature articles and annual reports.

Previous clinical information was obtained from the IND for the approved Gonal-f® formulation (IND 38,712) and from the NDA for the approved Gonal-f® formulation (NDA 20-378). The original clinical data and updates are incorporated into this review by cross-reference.

B. Tables Listing the Clinical Trials

The tables listing the original clinical trials for the currently approved Gonal-f® formulation were obtained from NDA 20-378. The tables from the currently approved Gonal-f® formulation were incorporated into this review by cross-reference. Additional tables listing the two submitted clinical studies, Studies 21884 and 22240, to demonstrate the non-inferiority of the new fill-by-mass r-hFSH formulation are contained in NDA 20-378 – Supplement SE8-032 (submitted 25 May 2003). Tables from the two submitted clinical studies were also incorporated into this review by cross-reference. Additional brief summaries of four previous pivotal clinical trials for the currently approved Gonal-f® formulation are summarized in Appendix 1 - A. Overview of Completed Clinical Trials for NDA 20-378.

C. Post-marketing Experience

Overseas post-marketing experience for the new r-hFSH formulation was not submitted with supplement SCF-015 or SCF-016 or in the electronic submission for the two clinical studies (Studies 21884 and 22240).

The most current periodic Annual Report for the currently approved Gonal-f® formulation was submitted to NDA 20-378 (P-015 dated 25-Nov-03) for the time period from 23 Sep 2002 through 22 Sep 2003. In this current Annual Report, the sponsor stated that the currently approved Gonal-f® formulation has not been withdrawn or suspended for any reason during the past year. The serious adverse event data obtained from the most recent Annual Report for NDA 20-378 (P-015) included:

- 1 case of a pulmonary embolism (in a patient with a history of a positive anticardiolipin antibody)
- 2 cases of thromboembolic disease (associated with ovarian hyperstimulation syndrome)
- 3 cases of ovarian hyperstimulation syndrome (2 were hospitalized for complications)

The sponsor stated that there was one death after a cardiac arrest during use of the currently approved Gonal-f® formulation during the reporting period. However, this case is under police investigation and no further information is available. Several different dosage strengths of the currently approved Gonal-f® formulation are marketed around the world including the European Union, South America and the United States. (2001 Annual Report to IND 38,712 (N105-YY) dated 28 Mar 2002.

D. Literature Review

Published literature articles referred to in this review document are included in Appendix 1 – B. References.

V. Clinical Review Methods

A. How the Review was Conducted

Two clinical studies were submitted to assess the non-inferiority of the new fill-by-mass Gonal-f® formulation (r-hFSH), submitted in electronic format on 23-May-03. The first clinical study was titled: "A phase III, multi-center, multi-national, randomized, assessor blind study to compare the safety and efficacy of a new formulation of recombinant human FSH (r-hFSH) versus Fertinex® versus Gonal-f® in stimulating multiple follicular development prior to ART in patients pretreated with GnRH agonist." This clinical study is identified as study 21884.

The second clinical study conducted was titled: "A phase III, prospective, randomized, assessor blind, multi-center, multinational comparative trial of a new formulation of r-hFSH versus Fertinex® and Gonal-f® in oligo-anovulatory infertile women undergoing ovulation induction". This clinical study is identified as study 22240.

B. Overview of Materials Consulted in Review

This review contains direct reference to:

- The original Medical Officer's Review of Gonal-f® dated 03-Mar-94
- The protocols for study 21884 (original protocol received 20-Mar-00) and study 22240 (original protocol received 20-Feb-01) were submitted to IND 38,712.
- The original Clinical Pharmacology and Biopharmaceutics review dated 22-Mar-01
- The Medical Officer's Review of a Safety Update submitted to IND 38,712 covering the period 01-Dec-01 through 30-Nov-02.
- The Statistician's Protocol review of study 21884 dated 15-Mar-00.

Previous clinical data obtained from the original NDA for the approved Gonal-f® product (NDA 20-378) were cross-referenced. (See Appendix 1 – A. Overview of Clinical trials for NDA 20-378). In addition, published literature references in this review are listed in a separate addendum (Appendix 1 – B. References).

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The appropriate DSI audits in the original NDA (20-378) for the approved Gonal-f® formulation were conducted in April of 1997. No problems were noted in the NDA application at that time. Therefore, in 1997, DSI concurred with the recommendation that all clinical studies be accepted in support of NDA 20-378.

New DSI audits for clinical studies 21884 and 22240 were completed between September and November 2003, and no problems were noted in the DSI inspections performed. Therefore, in 2004, DSI concurred with the recommendation that all clinical sites be accepted in support of the supplemental application for the new r-hFSH formulation.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Sample patient informed consent forms were submitted electronically for the two clinical studies (21884 and 22240) and appear adequate. The sponsor reported that the patient informed consent and investigator brochures were reviewed and approved by the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC). In addition, the sponsor provided a list of the IRBs/IECs that granted the original approval of studies 21884 and 22240.

E. Evaluation of Financial Disclosure

The financial disclosure statement (FDA 3454) for the new formulation of Gonal-f® (r-hFSH) has been completed and certified by the applicant.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In this reviewer's opinion, the new formulation of Gonal-f® (r-hFSH) has demonstrated clinical non-inferiority to approved gonadotropin formulations for the proposed indications in women. Clinical non-inferiority of the new r-hFSH formulation to Gonal-f® supports the proposed labeling claim for ovulation induction and clinical non-inferiority of the new r-hFSH formulation to Fertinex® supports the proposed labeling claim for multiple follicular development in women that are approved for the original formulation of Gonal-f®.

B. General Approach to Review of the Efficacy of the Drug

Previously submitted efficacy data for the approved Gonal-f® formulation supported two separate indications in women: multiple follicular development in an assisted reproductive technology program and induction of ovulation in anovulatory infertile women. (See the original Medical Officer's review of NDA 20-378 dated 03-Mar-94, and Medical Officer's Original Summaries of Amendments for the current approved Gonal-f® product dated 18-Apr-96, 26-Nov-96, and 13-Feb-97).

Clinical non-inferiority of the new Gonal-f® formulation (r-hFSH) is demonstrated in two submitted clinical studies, one for each proposed indication.

- Study 21884: The first clinical study for the proposed indication in women undergoing ART.

- Study 22240: The second clinical study for the proposed indication in anovulatory women undergoing ovulation induction.

General Approach to the Review of the Efficacy of the Drug (continued):

Study 21884 supports the first proposed labeling claim for the new r-hFSH formulation in treatment in women undergoing assisted reproductive technologies (ART) using either in vitro fertilization (IVF) or with intracytoplasmic injection (ICSI). Study 21884 demonstrates the non-inferiority of the r-hFSH formulation to the Fertinex® formulation on a clinical efficacy endpoint by use of the lower bound of the 95% confidence interval. . The clinical primary efficacy endpoint is the difference between r-hFSH and Fertinex® in mean number of fertilized (2PN) oocytes per patient.

Reviewer's comment on ART study 21884: The final protocol for study 21884 included a co-objective of confirming the non-inferiority of the new Gonal-f® (r-hFSH) formulation and Fertinex® [redacted] using a "step-down" approach. Both the statistician and primary Medical Officer concurred that the "step-down" approach in the Protocol Amendment was acceptable.

Study 22240 supports the second proposed labeling claim for the new Gonal-f® formulation (r-hFSH) in oligo-anovulatory infertile women undergoing ovulation induction (OI). The protocol for Study 22240 was submitted on 20-Feb-01 and reviewed by the Medical Officer and Statistician. The protocol for study 22240 was designed to evaluate the clinical non-inferiority of r-hFSH in comparison to the approved Gonal-f® as assessed by the ovulation rate in the first cycle of treatment.

The sponsor defined the ovulation rate as the percentage of women in the first cycle that ovulated (as defined by a mid-luteal progesterone ≥ 10 ng/ml and/or patients that became clinically pregnant). Study 22240 defined non-inferiority of the new r-hFSH formulation to the approved Gonal-f® formulation based on a two-sided 97.5% confidence interval (between –20% and 20%, inclusive).

Reviewer's comment on OI study 22240: The original protocol for study 22240 included a co-objective of

. The sponsor amended the protocol for OI study 22240 to delete the from the study, and therefore decrease the sample size required for the study (Protocol Amendment 2 dated 22-Oct-01). This Amendment was not submitted to the Division for review.

C. Detailed Review of Trials by Indication

Study 21884

Study 21884 began on July 2000 and was completed in June 2001.

Study title: "A phase III, multi-center, multi-national, randomized, assessor blind study to compare the safety and efficacy of a new formulation of recombinant human FSH (r-hFSH) versus Fertinex® versus Gonal-f® in stimulating multiple follicular development prior to ART in patients pretreated with GnRH agonist."

Investigator/Location: This study was conducted at 34 centers throughout the United States and Argentina. 32 centers enrolled at least one patient. Please refer to Appendix 1 – C. Principal investigator list.

Study rationale: The sponsor's letter (Dated 17-Mar-00) for the first study protocol submitted (21884) stated in the attached sponsor's letter that " That it is our intention to conduct clinical studies in ART, comparing the new formulation of Gonal-F® with the currently marketed formulation and the currently marketed, highly purified urinary FSH, Fertinex®. We are planning to conduct this three-way comparative clinical trial [Protocol No. 21884] in parallel with the bioequivalence study in the event that we are unable to demonstrate bioequivalence and in order to update our package insert with more current and relevant clinical data.

The sponsor also stated in the March 2000 letter that

Study objective(s): The initial protocol for study 21884 (submitted with the sponsor's letter dated 17-Mar-00) stated that the primary objective of the study was:

- [redacted]

The study protocol (21884) was reviewed by both the Medical and Statistical Reviewer. The sponsor received comments on the protocol (Letter dated 31-May-00). In the May 2000 letter, the sponsor was asked to clarify whether the purpose of the study was [redacted] or support efficacy of the new formulation compared to Fertinex®. On 09-Aug-00, the Division received the final revised protocol for clinical study 21884. The changes to the protocol for study 21884 were in response to the Division's written comments and questions (Division letter dated 31-May-00). The revised protocol proposed a stepped approach to demonstrating efficacy of the new r-hFSH formulation.

The sponsor's revised final primary "step-down" objectives for study 21884:

- [redacted]
- [redacted] non-inferiority of new r-hFSH formulation compared to Fertinex® would be demonstrated if the lower limit of the 95% confidence interval of the difference in mean number of fertilized oocytes (2PN) is higher than -1 fertilized oocyte".

The revised primary co-objectives for study 21884 were accepted by the Medical Officer on 11-Aug-00 and the Statistical Reviewer on 07-Mar-01.

Study design: Study 21884 was a prospective, randomized, assessor-blind, multi-center, multi-national comparative study that recruited infertile women undergoing assisted reproductive technology procedures [either patients undergoing *in vitro* fertilization (IVF) or patients undergoing *in vitro* fertilization with intra-cytoplasmic injection (IVF/ICSI)].

Method of assignment to treatment:

All patients received down-regulation using a gonadotropin releasing hormone agonist (Lupron®). Patients ready to begin treatment (after appropriate down-regulation measured by ultrasound and estradiol criteria) were randomized in a 1:1:1 ratio to receive one of the following gonadotropin treatments:

Method of assignment to treatment (continued):

- The new formulation of Gonal-f® (r-hFSH)
- The current approved formulation of Gonal-f® (r-hFSH)
- The approved formulation of Fertinex® (u-hFSH).

Each patient was assigned a unique centralized treatment randomization number. If a subject withdrew from the study prior to completion, her identification number was not reassigned.

The sponsor stated that randomization was stratified by center, age (up to 34 years old and 35 years old and above) and method of insemination (in vitro fertilization [IVF] or intracytoplasmic injection [ICSI]). The method of insemination (conventional IVF or ICSI) must be selected at the time of randomization prior to treatment initiation.

Reviewer's comments:

1. **The sponsor contends that patients undergoing insemination using IVF (in vitro fertilization) or IVF with an additional ICSI (intracytoplasmic injection) procedure have similar oocyte fertilization rates. The sponsor supports this contention of similar fertilization rates by quoting three published references. [3,4,5] The first two publications referenced by the sponsor are solely based on a sub-set of infertility patients with tubal factor who have normospermic partners.[3,4] In contrast, study 21884 did not restrict ICSI patients with tubal disease and normospermic partners. Furthermore, these two submitted clinical publications also have significant flaws in trial design in both randomization and primary efficacy endpoint prespecification.[3,4] These study design issues prohibit these two clinical studies from providing acceptable evidence of similar fertilization rates in the overall patient population undergoing IVF compared to those undergoing IVF with ICSI.**

2. **The additional abstract submitted by the sponsor to support similar fertilization rates between the two insemination types (IVF and ICSI) was not an appropriately designed comparative, randomized clinical study that could provide sufficient evidence of similar fertilization rates between the two types of insemination. Therefore, in this reviewer's opinion, the sponsor has not adequately demonstrated that patients undergoing IVF have similar fertilization rates to patients undergoing IVF/ICSI procedures in the general infertility population treated in study 21884. The sponsor has only presented limited evidence that the sub-population of ART patients with tubo-peritoneal factor may have similar fertilization rates for the two types of inseminations (IVF and ICSI).**

This reviewer recognizes that multiple publications have demonstrated that ICSI has a higher rate of oocyte fertilization in couples with male infertility than IVF. [6,7,8] In this reviewer's opinion, the increased fertilization rates may have shifted the numbers of fertilized oocytes because of the type of insemination procedure rather than a true gonadotropin effect. In addition, this reviewer concludes that if the sponsor had wanted to look at only a gonadotropin effect on oocyte fertilization, the sponsor should have limited ICSI to couples with tubal factor where the rates of oocyte fertilization are potentially similar for in vitro fertilization and intracytoplasmic injection.

Patient population: The final protocol for study 21884 stated that 700 patients were planned for enrollment to ensure that 669 evaluable patients (223 in each of the 3 hFSH treatment group). The completed study randomized a total of 713 patients, with a 711 receiving study treatment. The study treated 237 patients in the new r-hFSH group and 239 in the Fertinex® group, the two treatment groups pertinent to the primary efficacy objective of study 22240. Study patients were enrolled from 26 US sites and 6 sites in Argentina. The contribution of patients from each site to study 21884 varied from 0.008% (Center 15 with six treated patients) to 10% (Center 03 with seventy-four treated patients).

Reviewer's comment: One hundred and sixty six patients (23%) of the 711 treated patients were performed in clinics in Argentina. This reviewer has some concerns that the patient populations in Argentina may not be comparable to those recruited in the United States or Europe. Ninety percent of assisted reproductive technology (ART) sites in Latin America are private institutions with little or no university or government funding. The lack of funding for ART restricts access in Argentina to couples who can pay the high cost involved. In contrast, in parts of the United States and in Europe, third party payers such as insurance, university and government funding cover (directly or indirectly) a portion of the total cost of ART procedures. In this reviewer's opinion, the lack of access to ART treatment in Argentina may cause this population to be demographically different than other ART patient population recruited in the United States and Europe.

Duration of clinical treatment:

Patients undergoing an assisted reproductive technology cycle with in vitro fertilization or in vitro fertilization with intracytoplasmic injection could be treated for one cycle only.

Inclusion criteria (in final protocol):

1. Was an infertile woman wishing to conceive whose physician had recommended that she undergo ART (IVF or ICSI).
2. Was aged 18-39 (inclusive).
3. Had regular menstrual cycles every 25-35 days.
4. Male partner had a semen analysis with $\geq$ 2 million sperm/mL of ejaculate for IVF. If the patient's partner did not satisfy this criterion, ICSI was to be used. (Donor sperm was required for those patients that were considering ICSI or were being considered for ICSI).
5. Surgically retrieved spermatozoa (epididymal, testicular, fresh/frozen/thawed) could be used for ICSI.
6. Had a body mass index (BMI) < 35 kg/m^2.
7. Had both ovaries present.
8. Had a transvaginal ultrasound scan or HSG or hysterosonogram or hysteroscopy within six weeks prior to beginning GnRH agonist therapy showing no clinically significant uterine abnormality, which, in the Investigator's opinion, could have impaired embryo implantation or pregnancy continuation.
9. Had a normal cervical cytology within three years prior to beginning GnRH-agonist therapy.
10. If the patient had prior stimulation cycles, at least a 60-day washout period after the last dose of gonadotropin or clomiphene citrate, prior to beginning the administration of Lupron® for down-regulation.
11. Had a screening laboratory result for FSH that was less than the upper limit of normal for the early follicular phase at central laboratory.
12. Was willing and able to comply with the protocol for the duration of the study
13. Had voluntarily provided written informed consent, prior to any study-related procedure that was not part of normal medical care, with the understanding that the patient could withdraw consent at any time without prejudice to her future medical care.

Exclusion criteria (in final protocol):

1. Had a clinically significant systemic disease.
2. Was known to be infected with Human Immunodeficiency Virus (HIV).
3. Was known to be infected with Hepatitis B or C virus.
4. Had any medical condition which, in the judgement of the Investigator and sponsor, could have interfered with the absorption, distribution, metabolism or excretion of the study drug.
5. Had endometriosis Grade III-IV (ASRM classification).
6. Had any previous ART cycle indicating a poor response to gonadotropin stimulation (defined as retrieval of three oocytes or less).

Exclusion criteria (continued):

7. If in a previous ART attempt there were no motile sperm before or after the sperm processing with ejaculated, epididymal, testicular, fresh or frozen/thawed spermatozoa.
8. Had three or more previous consecutive ART cycles without a clinical pregnancy.
9. Had abnormal, undiagnosed, gynecological bleeding.
10. Had a known allergy or hypersensitivity to human gonadotropin preparations or any other study-related medications (for example: Lupron®, Profasi®, and Crinone® 8%).
11. Had known current substance abuse.
12. Had previously participated in this study or was simultaneously participating in another clinical trial
13. Had uni- or bilateral hydrosalpinx

Reviewer's comments:

- **The randomization scheme was revised by the sponsor in the protocol amendment (Serial No. 088 dated 09-Aug-00) to stratify patients according to insemination such that all subjects either got traditional IVF or ICSI.**
- **These changes in the protocol allowed that all subjects could potentially be treated with ICSI, not just those subjects with male factor infertility. This reviewer would have recommended that only subjects with tubal factor be included in the ICSI population (so that patients would have equivalent fertilized rates as compared to IVF).**
- **It is unclear why the final patient population had a larger percentage of patients had ICSI (approximately 60% in each treatment group) as compared to IVF. The impact of having an increased number of patients who had ICSI (approximately 60%) in a given treatment group (as compared to IVF) on the clinical outcome is unknown. However, ICSI has a higher fertilization rate for certain diagnoses (i.e. male infertility[6,7,8] and possibly fertilization failure and unexplained infertility[9,10]. The sponsor may have enriched patient population by including ICSI as an insemination type, and demonstrated overall higher fertilization rates than would be seen with IVF alone in previous studies.**
- **The sponsor included one patient in the efficacy comparison of r-hFSH to Fertinex® who had a documented hydrosalpinx during treatment. It is not anticipated that this single patient would have a significant impact on the overall study outcome, and this patient was included in the final efficacy analysis.**

Trial period: From July 2000 through June 2001.

Dosage and administration: All patients had pituitary down-regulation with a gonadotropin-releasing hormone agonist (Lupron®) confirmed with a serum estradiol level of ≤ 50 pg/mL and ultrasound.

The starting daily dose for patients younger than 35 years of age:

- The new r-hFSH formulation was started with a fixed dose of 10 mcg/day for five consecutive days.
- The approved Gonal-f® formulation was started with a fixed dose was 150 IU/day for the first five consecutive days.
- Fertinex® formulation (u-hFSH) was started at a fixed dose of 150 IU/day for the first five consecutive days.

Patients between 35 and 39 years of age (inclusive):

- The new r-hFSH formulation patients were started with a fixed daily dose of 15 mcg/day
- The approved Gonal-f® formulation (and Fertinex® (u-hFSH) treatment subjects) was started at 225 IU/day of the approved Gonal-f® formulation or Fertinex®.
- Dose adjustments were made from the sixth day onward based on individual patient response.

For all patients, regardless of age or type of insemination:

- The maximum daily dose for the r-hFSH formulation was 30 mcg/day.
- The maximum daily dose for the approved Gonal-f® and Fertinex® was 450 IU/day.

Reviewer's comments:

1. **The concept of increasing the starting FSH dose in patients over 35 has been used in clinical practice, but not in previous clinical studies for gonadotropin approval. Study 21884 was not powered to show whether at a given age cut-off there might be a difference in dose required. However, the dosing schedule used in study 21884 for patients over 35 should be identical to that recommended in the label.**
2. **The sponsor indicated that some centers split the patient's total daily dose when the patient required more than four ampules daily. This split dose would be given half of the dose in the morning and the other half in the evening. This split dose regimen was noted by the sponsor as part of the normal routine for some centers. The impact of this split dose on clinical outcome and endpoints is unknown.**

Treatment protocol: Patients who met the inclusion criteria began treatment with pituitary desensitization during the mid-luteal phase using subcutaneous Lupron® administration. Pituitary down-regulation was defined as a serum estradiol level of ≤ 50 pg/mL. In addition, an initial transvaginal ultrasound at the time of pituitary down-regulation was used to confirm that the patient did not have pre-existing ovarian cysts or follicles. If the transvaginal ultrasound and serum estradiol were achieved, gonadotropin therapy was initiated. Gonadotropin and Lupron® therapy was continued until the criteria for hCG (Profasi® 10,000 IU) was met.

Oocytes were retrieved approximately 34-36 hours after hCG administration, and then were assessed and fertilized using IVF or IVF/ICSI. No more than 3 embryos or 2 blastocysts will be replaced. Oocyte, embryo and final outcome assessments were made for all patients.

Patients who had intrauterine insemination therapy (instead of insemination with in vitro fertilization or intracytoplasmic injection) were excluded from the efficacy analysis. In addition, patients that had mixed insemination (oocytes insemination with both in vitro fertilization and intracytoplasmic injection [i.e. mixed inseminations] were excluded from therapy). Luteal phase support was daily vaginal administration of Crinone® (progesterone gel, 8%) starting on the day of the procedure (or the day after the procedure) up to menstruation. Patients were allowed to donate and/or cryopreserve embryos. If the patient (or donor) became pregnant, the progesterone was continued for at least 30 days after the pregnancy was confirmed by laboratory evidence.

Reviewer's comments on patient treatment protocol:

1. **The sponsor's stated primary efficacy analysis (in the original and amended protocols for study 21884) is the comparison of r-hFSH and Fertinex®.**
2. **The primary efficacy analysis included ten patients who completed therapy despite violations of the standards outlined in the protocol. These ten patients had deviations that included:**
    - **Eight patients with down-regulated serum estradiol values of greater than the cut-off level of ≤ 50 pg/mL**
    - **One patient who received more than four embryos**
    - **One patient who had a hydrosalpinx at entry**

    However, in this reviewer's opinion, the impact of these patients (Less than 2% of the total patients treated with the new r-hFSH or Fertinex®) on the overall efficacy analysis would be clinically insignificant.

Demographic and baseline characteristics:

Treatment groups were similar with respect to most baseline characteristics for the new r-hFSH treatment arm and the Fertinex® treatment arm. Demographic and baseline characteristics are reported in Appendix 2 – Tables 1A, 2A, 3A and 4A.

Baseline characteristics included:

- Mean patient age was 32 years in both the r-hFSH and Fertinex® treatment arms.
- Mean weight was 63 kg in the r-hFSH and Fertinex® treatment arms.
- A similar racial profile for study 21884 in both the r-hFSH treatment arm and the approved Gonal-f® treatment arm.
- Mean duration of infertility of 4 years in both the r-hFSH and Fertinex® treatment arms.
- Mean sperm concentration of 54 million sperm per ml in both the r-hFSH and Fertinex® treatment arms.
- Mean serum FSH level of 7 mIU/mL in both the r-hFSH and Fertinex® treatment arms.

Other patient characteristics including main cause of infertility, smoking habits, type of infertility and other semen analysis parameters (including morphology and motility) were compared between the r-hFSH and Fertinex® treatment arms.

No statistically significant differences were seen in any of the demographic or baseline characteristics between the new r-hFSH and Fertinex® treatment groups.

Reviewer's comments:

1. **This reviewer has concerns about the significant percentage of patients treated in this study for a primary diagnosis of male infertility (approximately 50% of the treatment group). The numbers of patients with male infertility appear to be higher than seen in previous IVF studies performed several years ago. This reviewer has significant concerns that increasing the number of patients with male infertility that are treated with ICSI may increase the fertilization rates (the primary endpoint in this study) because of the ICSI procedure, and not from the use of the gonadotropin.**
2. **Sperm morphology reports were listed as "missing" in 48% of patients treated in both in the r-hFSH and Fertinex® treatment arms(See Appendix 2 – Table 3A) It is unknown if inclusion of these "missing" morphology reports in the analysis of the baseline characteristics would have generated a statistical imbalance between the two treatment groups.**

Down-regulation of the pituitary axis as measured by serum estradiol levels for study 21884 demonstrated (See Appendix 2 – Table 5A):

Reviewer's comment: There was no statistical significant difference in down-regulated estradiol levels in the intent-to-treat patient population between the r-hFSH treatment arm and the approved Gonal-f® treatment arm. In addition, no statistically significant differences were noted between the r-hFSH treatment arm and the approved Gonal-f® treatment arm when the groups were stratified by age.

Primary efficacy assessment:

The primary efficacy endpoint designated by the sponsor was the total number of fertilized oocytes in the first treatment cycle (see Amendment 1 dated July 12, 2000). All oocytes with 2 pronuclei observed the day after fertilization (day 1 after ovum pickup) would be counted. In the final accepted protocol for study 21884, the sponsor stated:

1.

2.

3. A second statistical analysis would occur if the test of statistical significance fails to show that

   This second step will be envisaged in order to establish the equivalence (in terms of non-inferiority) between the new r-hFSH formulation and Fertinex®.
4. "Clinical equivalence" (in terms of non-inferiority) would be declared if the lower limit of the 95% confidence interval of the difference [new r-hFSH formulation – Fertinex®] is higher than minus one fertilized oocyte.

The sponsor designated multiple secondary efficacy endpoints including:

- Cumulative dose of FSH used
- Duration of FSH treatment
- Number of follicles ≥ 11 mm and ≥ 14 mm on the day of hCG, treatment days 6 and 9.
- Proportion of patients that received hCG/egg retrieval/embryo transfer

Secondary efficacy endpoints (continued):

- Number of total/metaphase II oocytes retrieved /oocytes inseminated/embryos/frozen embryos
- Total, biochemical, ectopic and clinical pregnancy rate
- Serum estradiol levels at hCG day
- Zona pellucida (proportion intact)/Nuclear maturity/Stage of fertilization/Embryo grading/number of blastomeres

Protocol violations and other allocation issues:

Study 21884 enrolled 837 total patients, 124 total patients were discontinued from the study prior to randomization. Seven hundred eleven patients (84.9%) were randomized in study 21884 to the three treatment groups (r-hFSH, the approved Gonal-f® or Fertinex®) and received FSH treatment.

Patients evaluated in the primary efficacy analysis included 474 total patients that were randomized and received at least one dose of either r-hFSH or Fertinex®. Of note in these two treatment arms:

- 464 patients (97.9%) received hCG administration
- 459 patients (96.8%) had evaluable 2PN oocytes on day one after ovum pickup

Reviewer's comment: Twenty-two percent (189 of 837) were discontinued prior to completion of the ART procedure. (See Appendix 2 – Table 6A) Although this number appears high, it is close to the actual clinical cancellation rate for ART procedures in the U.S [14%].[11]

a. Randomization violations in all three treatment groups:

A total of 64 of the 711 (9%) of treated patients had randomization errors. The reasons for discontinuation included: 33 who changed insemination methods, 29 who had mixed inseminations and 2 who had IUI's.

- 26 patients were randomized to have IVF but had ICSI
- 7 patients were randomized to have ICSI but had IVF
- 29 patients had mixed inseminations
- 3 patients were wrongly allocated in the < 35 years strata
- 1 patient was wrongly allocated in the ≥ 35 years strata

b. Treatment violations

A total of 13 of the 711 (2%) of treated patients had randomization errors. The reasons for the violation included:

- 3 patients were wrongly allocated in the wrong formulation
- 10 patients did not meet the hCG administration criteria (2 in the new r-hFSH group and 1 in the Fertinex® group, 7 in the approved Gonal-f® group)
- 2 patient had no confirmation of down-regulation of estradiol levels (1 in the Fertinex® group and 1 in the approved Gonal-f® group)
- 1 patient received more than 8 ampules of gonadotropin daily (in the approved Gonal-f® group)

c. Discontinuation prior to hCG:

A total of 20 patients were discontinued from treatment during gonadotropin therapy, 17 of the 20 subjects from r-hFSH or Fertinex® prior to hCG administration. The discontinued patients included ten patients in the r-hFSH treatment arm and 7 in the Fertinex® treatment arm. The reasons for discontinuation prior to hCG included:

- Inadequate ovarian response (8 patients in the r-hFSH group, 5 in the Fertinex® group, 2 in the approved Gonal-f® group)
- Adverse event (One patient in the r-hFSH arm was discontinued after being diagnosed with appendicitis, one patient in the approved Gonal-f® group was discontinued for the risk of ovarian hyperstimulation syndrome)
- Two patients decided to withdraw from the study (one from the r-hFSH group and one from the Fertinex® group)
- One patient in the Fertinex® group took her Profasi® at the wrong time (protocol violation and had no oocytes).

d. Post retrieval (No embryo transfer):

33 patients did not have an embryo transfer.

- 17 patients had no fertilization (Five patients in r-hFSH group, 5 in the Fertinex® group and 7 in the approved Gonal-f in the approved Gonal-f® group).
- 14 had poor or no embryo development (Seven patients in the r-hFSH group, 5 in the Fertinex® in the approved Gonal-f® group and 2 in the Gonal-f® in the approved Gonal-f® group.

Post retrieval (continued):

- 1 patient had all her embryos frozen in the new r-hFSH group because of the risk of OHSS.
- 1 patient had no blastocyst development in the approved Gonal-f in the approved Gonal-f® group.

Reviewer's comments:

1. **This reviewer notes that in the two primary efficacy groups (r-hFSH and Fertinex®) 18 patients had randomization violations where the patients were randomized to one insemination type, but received another type (4%).**

These numbers of randomization to one type of insemination, but treatment with another would appear to be roughly similar. However, it is clear that not all infertility diagnosis have equivalent rates of fertilization for IVF and ICSI. Male infertility (ranging from subfertile to severe) has higher fertilization rates when ICSI is used. [6,7,8] Therefore, this reviewer also evaluated the diagnosis of patients that converted from IVF to ICSI.

- **Six of these twenty patients with randomization violations (who were in the two primary efficacy groups) presented with tubo-peritoneal disease.**
- **Of the patients in both groups that were converted from IVF to ICSI, 2 patients in the Fertinex® group and 3 patients in the r-hFSH group had male factor as part of the diagnosis.**

In conclusion, it does not appear as if the number of patients or the type of patients with male factor converted to ICSI significantly altered the treatment groups. However, the sponsor should re-evaluate the use of ICSI in gonadotropin protocols as the fertilization rates impact fertilization rates.

2. **The sponsor excluded subjects with mixed insemination procedures. This reviewer concurs with the sponsor's assessment, since these patients could not be stratified.**
3. **Other protocol violations noted by the reviewer included: not achieving the stated down-regulated serum estradiol level as specified in the protocol (eight patients), receiving more than 4 embryos (one patient) and having a hydrosalpinx at study entry (one patient).**

In this reviewer's opinion, study 21884 has a significant number of patients who had randomization or protocol violations (11%). In addition, only 649 patients (91%) of the 711 treated with gonadotropins achieved embryo transfer. However, the number of patients who were discontinued was not significantly different between treatment groups. (p=0.19)

Primary efficacy evaluation:

The sponsor's designated primary efficacy endpoint was the number of fertilized oocytes. The primary efficacy analysis was a stepwise procedure where 1) [redacted] and then non-inferiority was to be shown. [redacted] If these criteria were not met, then non-inferiority would be shown if the lower bound of the 95% confidence interval is greater than -1 oocyte. The intent-to-treat population was defined as all patients who were randomized and received at least one injection of FSH, was analyzed.

The sponsor's analysis of the mean fertilized oocytes resulted in:

- 6.7 fertilized oocytes for the r-hFSH formulation
- 6.0 fertilized oocytes for the Fertinex® formulation
- A mean difference of 0.74 fertilized oocytes between the new r-hFSH and Fertinex® groups (a larger mean number of fertilized oocytes with r-hFSH) with a two-sided 90% confidence interval (0.11, 1.36)

Reviewer's comments: It is not clear why the sponsor presented a 90% two-sided confidence interval except that they assumed a 95% one-sided confidence interval (which would give the same lower bound). According to the sponsor's results, [redacted], but r-hFSH is non-inferior to Fertinex® (because the lower bound of the confidence interval is greater than -1 oocyte). The Statistician and Medical Reviewers noted that the data was skewed, and therefore, medians were used to examine the differences between these two efficacy treatment groups. In addition, the ITT group was analyzed using the insemination treatment the patient received, not the treatment the patient was randomized to. The reviewer's ITT population consisted of a total of 474 patients (See Appendix 2 – Table 7A). The ITT population was analyzed using the treated the patient actually received, not the treatment patients were randomized.

In addition, it is not clear what the sponsor's two-sided 95% confidence interval would have been if and if the lower limit would be greater than -1 oocyte. So the Statistical Reviewer calculated a two-sided 95% confidence interval, which is what the Division typically requires.

Reviewer's comments (continued):

The reviewer's analysis of the median number of fertilized oocytes resulted in:

- **6 fertilized oocytes per patient retrieval for the r-hFSH formulation**
- **5 fertilized oocytes per patient retrieval for the Fertinex® formulation**
- **A median difference of 1 fertilized oocyte between the new r-hFSH formulation and Fertinex® groups.**

The Statistician's analysis shows that the lower bound of the two-sided 95% confidence interval of the difference between the two treatment groups [new r-hFSH minus Fertinex®], using the median number of fertilized oocytes, was greater than minus one oocyte for both the overall ITT and evaluable populations in both the sponsor's and reviewer's analysis. (See Appendix 2 - Tables 7A and 8A). The evaluable patient was analyzed removing patients who underwent mixed inseminations and intrauterine inseminations. In addition, patients who did not receive hCG and did not undergo oocyte retrieval were also removed.

1. **It was expected that the stratification of the type of insemination would have resulted in an equal distribution of IVF and ICSI patients between the two primary efficacy treatment groups. However, the sponsor did not specifically state in the protocol or protocol amendment that the stratification of patients in each treatment group of IVF and ICSI patients would be equivalent (i.e. 1:1). In the two primary efficacy treatment groups, it is apparent that there were a larger number of patients that received ICSI (approximately 60% in each treatment group).**

   In this reviewer's opinion, the overall IVF patient population appears have slightly less fertilized oocytes in the r-hFSH group (Mean 6.4 fertilized oocytes compared to a mean of 6.9 for the ICSI patient population) in this study. Since there are more ICSI patients than IVF, the ICSI patients, the sponsor may have improved the overall outcome measure by increasing the number of ICSI patients, and therefore, increasing the number of overall fertilized oocytes.
2. **A secondary analysis of the primary efficacy endpoint was performed using the evaluable patient population (removing patients that had randomization or protocol violations, except for patients that had tubal disease and were incorrectly randomized). This secondary analysis of the primary efficacy endpoint did not change the study outcome. (See Appendix 2 – Table 8A)**

Reviewer's comments (continued):

3. **Three secondary analysis of the primary efficacy endpoint by type of insemination (*in vitro* fertilization [IVF] or intra-cytoplasmic injection [ICSI]) and by country, by age and type of insemination, and by country and type of insemination were performed to see if there were significant effects on the final analysis:**

    a. **Analysis of the primary efficacy endpoint separated by type of insemination showed that the new r-hFSH formulation is non-inferior to Fertinex® for the number of fertilized oocytes for overall two efficacy treatment groups for ICSI, and borderline for IVF. (See Appendix 2 – Table 8A)**
    b. **Analysis of the primary efficacy endpoint in patients under age 35 showed that the new r-hFSH formulation is non-inferior to Fertinex® for the number of fertilized oocytes for each insemination type.**
    c. **In contrast, in the age group 35 and older, the new r-hFSH formulation is worse than Fertinex® for the number of fertilized oocytes for each insemination type. The mean numbers of fertilized oocytes were consistently lower in the r-hFSH treatment group compared to the Fertinex® treatment group.**
    d. **For Argentina, only the ICSI group showed that the new r-hFSH formulation is non-inferior to Fertinex® for the number of fertilized oocytes. (See Appendix 2 – Table 9A)**
    e. **Analysis of the primary efficacy endpoint by country that the new r-hFSH formulation is non-inferior to Fertinex® for the number of fertilized oocytes in the U.S. for each insemination type See Appendix 2 – Table 10A) .**

This reviewer also notes are significantly less fertilized eggs in both the IVF and ICSI procedures (mean of 4.7 for IVF and mean of 4.9 for ICSI) performed in Argentina compared to the United States (mean of 6.7 for IVF and mean of 7.0 for ICSI) (Appendix 2 – Table 11A). Several hypotheses may explain these differences in the primary efficacy endpoints observed in the two countries including: different laboratory protocols, different equipment used, and different patient populations. The reason(s) for this difference in fertilized oocytes between countries is unknown.

Secondary efficacy parameters:

Three secondary efficacy parameters (total oocytes retrieved, metaphase II oocytes retrieved and embryos) were evaluated to see if significant differences occurred between the two treatment groups (r-hFSH and Fertinex®) for these parameters.

Results for Three Secondary Efficacy Parameters

	r-hFSH group	Fertinex® group
Mean number of total oocytes retrieved	11.9	10.7
Mean number of metaphase II oocytes retrieved	8.3	7.6
Mean number of embryos	6.5	5.7

Source: Appendix 2 – Tables 12A, 13A, 14A.

Reviewer's comments:

a. **There are clinical differences seen in the numbers of total oocytes, metaphase II oocytes or embryos observed between the two treatment groups.**
b. **In addition, there does not appear to be a clinical difference in the number of total oocytes or the number of embryos retrieved between treatment groups when analyzed by type of insemination (IVF or ICSI) (Appendix 1 – Tables 12A and 14A).**
c. **Sub-set analysis suggest that there may be a statistically increased number of total oocytes and embryos obtained in patients under 35 with use of the new r-hFSH compared to Fertinex®. (Appendix 2 – Tables 12A and 14A) The increased number of total oocytes and embryos may result from differences in response to the new r-hFSH compared to Fertinex® in this age group. It is not clear that this increased response (measured by total oocytes and embryos translates directly into an improved pregnancy rate in this age group.**
d. **The approved Gonal-f® treated group had a clinically similar mean number of fertilized oocytes (5.9) and median number of fertilized oocytes (5) as the Fertinex® group. Although not a primary efficacy comparison, the overall clinical outcome for mean and median number of fertilized oocytes would appear to be clinically similar for r-hFSH compared to the approved Gonal-f® formulation.**

The single most important efficacy variable for a patient undergoing Assisted Reproductive Technology (ART) procedures with gonadotropin therapy is the clinical pregnancy rate (as defined by a livebirth). The sponsor defined clinical pregnancy rate as the number of patients with one or more fetal sacs – with or without heart activity.

Reviewer's comment: The sponsor defines a clinical pregnancy rate definition of a fetal sac. The Division recommends that the definition of a clinical pregnancy rate should be a fetal sac with a heartbeat the current definition of a clinical pregnancy.

Study 21884 had a clinical pregnancy rate of 32.4% in the two evaluable patient groups treated with r-hFSH or Fertinex® therapy who received in vitro fertilization (IVF) or in vitro fertilization/intracytoplasmic injection (IVF/ICSI) procedures. This clinical pregnancy rate is consistent with the 2001 national clinical pregnancy rate averages seen in the United States (27%). [11]

The clinical pregnancy rate data is seen in Appendix 2 – Table 15A:

- 70 clinical pregnancies (29.8%) using the r-hFSH formulation
- 83 clinical pregnancies (35.0%) using the approved Fertinex® formulation.

There were no obvious clinical differences seen in the number of pregnancies when stratified by age or type of treatment (See Appendix 2 – Table 15A)

The livebirth pregnancy rate data is seen in Appendix 2 – Table 16A:

- 57 livebirths (24.3%) using the r-hFSH formulation
- 74 livebirths (31.2%) using the approved Fertinex® formulation.

Reviewer's comments:

1. **The clinical pregnancy rate (excluding patients who had intrauterine inseminations, as this has a separate pregnancy rate from other ART patients) is not clinically different between the r-hFSH group and the Fertinex® group. In this reviewer's opinion, this clinical pregnancy rate data suggests although gonadotropin therapy may have some impact on secondary efficacy endpoints such as embryos or oocytes, improvements in these laboratory endpoints may not translate into clinical pregnancies. However, study 21884 was not powered to demonstrate a difference in clinical pregnancy, so the actual differences in pregnancy rates between r-hFSH and Fertinex® groups are unknown.**
2. **A per protocol analysis of other pregnancy related outcomes were analyzed including ectopic pregnancy, miscarriages and multiple gestation. (Appendix 2 – Tables 17A and 18A). The per protocol analysis was performed to see if there were clinically apparent differences in these pregnancy related outcomes without confounding variables.**

Reviewer's comments (continued):

3. **The pregnancy outcomes for the treatment groups were compared for numbers of ectopic pregnancies, miscarriages or multiple gestations between the two formulations (Appendix 2 – Tables 17A and 18A). Intrauterine insemination and mixed insemination patients were excluded from the clinical pregnancy outcome data. No differences were found between the new r-hFSH and Fertinex® treatment in these secondary pregnancy related outcomes.**

In this reviewer's opinion, there seems to be no evidence for the majority of patients that the two treatments differ in the desired outcome of clinical pregnancy, However, this study was not powered to detect differences in clinical pregnancy rates between the two formulations, so it is difficult to draw a conclusion based solely on this limited pregnancy data.

Treatment exposure was significantly different ($p<0.01$) between the two groups

Results for Treatment Exposure

	r-hFSH group	Fertinex® group
Mean number of ampules (total)	26.2	29.1
Mean duration of treatment (days)	9.8	10.2

Source: Appendix 2 - Tables 19A.

Reviewer's comments:

1. **It was expected that the mean number of ampules and duration of use would be the same for both treatment groups (r-hFSH and Fertinex®). It is surprising that the r-hFSH group was statistically different than the Fertinex® group for both total ampules used and means duration of treatment. The explanation for this difference is seen in the sub-analysis of patients under 35 years old (Appendix 2 - Table 19A).**
   Patients under 35 years of age treated with r-hFSH had a appeared to demonstrate a clinically shorter duration of use and less total number of ampules than patients in the Fertinex® group, that is not seen in patients 35 years of age and older.
2. **These differences in duration and total FSH requirement in younger patients may indicate a difference in response in this sub-population to the new r-hFSH formulation. In this reviewer's opinion, it is unclear why this difference exists in the two treatment groups in the younger population, however, the differences do not appear to be clinically of concern.**

Study 22240

Study 22240 began on April 2001 and enrollment ended in November 2001 for the sites in the United States and January 2002 for sites in Argentina. Thee study was completed in July 2002.

Study title: "A phase III, prospective, randomized, assessor blind, multi-center, multinational comparative trial of a new formulation of r-hFSH versus Fertinex® and Gonal-f® in oligoanovulatory infertile women undergoing ovulation induction".

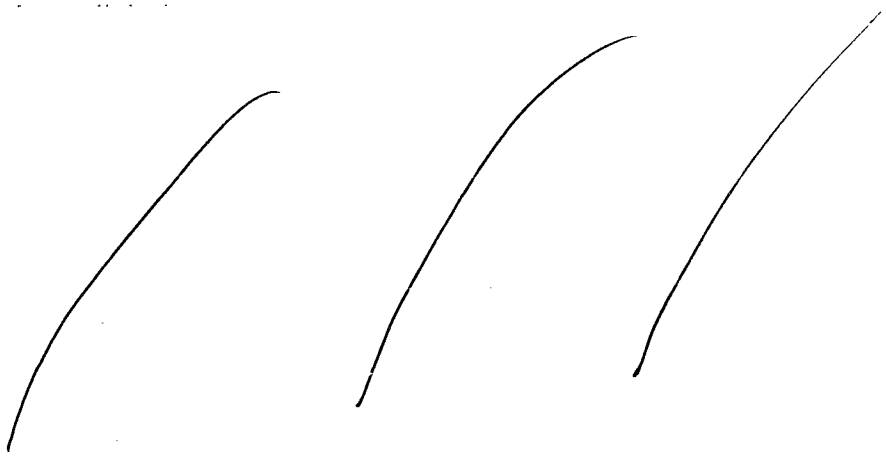
Investigator/Location: This study was conducted at 36 centers throughout the United States and Argentina. (Please refer to Appendix 1 – D. Principal investigator list).

Study rationale: The original rationale of the study was to assess the safety and efficacy of the new r-hFSH formulation compared to the currently approved Gonal-f® formulation when used for the induction of ovulation in women with oligo-anovulatory infertility. (submitted to IND 38,712 PN-094 submitted 20 Feb 2001)

Study objectives:

The original stated primary objectives of this study as stated by the sponsor were to evaluate:

- "The clinical equivalence of the new r-hFSH formulation to Gonal-F® as assessed by ovulation rates and the cumulative dose of FSH required in the first cycle of treatment".



Two additional amendments to the protocol for study 22240 were introduced by the sponsor as a result of data obtained from study 21884. These two Amendments (Amendment 1 dated 06 Aug 2001 and Amendment 2 dated 22 October 2001) were dated prior to the completion of study 22240 (15 July 2002). The purpose of these two Amendments were to revise the objectives of study 22240 to only demonstrate non-inferiority of new formulation of r-hFSH formulation to the approved Gonal-f® formulation

Other study protocol changes included:

- Broadening the patient population to include insulin resistant patients with fasting insulin levels up to 25 μU/mL
- Omit the washout requirements for insulin-sensitizing agents
- Elimination of comparison testing between the new r-hFSH formulation and Fertinex®.
- Changing the sample size to reflect
- Changing the analysis of the primary efficacy endpoint (ovulation rate) to a single non-inferiority comparison between r-hFSH and the approved Gonal-f® formulation.
- Adding an interim analysis section.

Reviewer's comments:

1. **Several of the changes noted in the Amendments had significant impacts on the study design and outcome data.**
   - **The original protocol for study 22240 stipulated a sample size of 519 subjects. The sponsor revised the protocol for study 22240 to a change in power from 94-95% to 80% and use a one-sided significance level of 5%. This change in power and significance level decreased the number of patients required to show the non-inferiority to 240 total subjects. The rationale for the sample size given by the sponsor was to remove of the objective to**
   - **The sponsor has broadened the oligo-anovulatory patient population by inclusion of insulin resistant patients with fasting insulin levels up to 25 μU/mL rather than a normal insulin level.**
   - **In addition, no washout period or discontinuation period was required if patients were taking insulin-sensitizing therapy.**

Reviewer's comments (continued):

- **In the two primary efficacy treatment groups:**
  - **7 of 95 subjects (7.4%) in the approved Gonal-f® group were treated with concomitant insulin-sensitizing therapy.**
  - **7 of 84 subjects (8.3%) in the r-hFSH group were treated with concomitant insulin-sensitizing therapy.**

In this reviewer's opinion, the sponsor should have either:

- **Required that patients should have discontinued insulin-sensitizing agents before entering the study protocol.**

Or

- **Stratified patients for use of insulin-sensitizing agents**

The patients treated with insulin sensitizing agents appear to be equally distributed between the two groups. However, this reviewer has concerns that the ovulation rates seen in these two treatment groups were improved slightly by the use of insulin-sensitizing agents. Although insulin-sensitizing agents are not approved in the United States for ovulation induction, it is clear that they significantly improve clinical outcomes when used with gonadotropins. [12,13]

In this reviewer's opinion, the sponsor has inadvertently altered the anovulatory patient population by introducing the use of these agents, and therefore, data from previous clinical studies is not comparable. Furthermore, although only 7% of the two efficacy treatment groups used insulin-sensitizing agents, it is unclear what impact that had on the overall ovulation rates.

Study design: Study 22240 was a prospective, randomized, assessor-blind, multi-center, multi-national comparative study that recruited oligo-anovulatory infertile women undergoing ovulation induction. The assessing physician, ultrasonographer and the team were blinded to the treatment allocated to each patient.

Method of assignment to treatment: Within three days after menses onset (natural or induced), patients who were ready to begin treatment were to be randomized (in a 1:1:1 ratio) to one of three treatment arms: new Gonal-f® formulation (r-hFSH), Fertinex® (a urinary-derived follitropin) or the approved Gonal-f® formulation. Each patient was allocated a unique treatment randomization number in sequential chronological order within the center. The study coordinator would then complete a randomization form and call a toll-free number for randomization to one of the three arms.

If a subject withdrew from the study prior to treatment completion, her treatment randomization number was not reassigned. The sponsor stated that randomization was stratified by center.

Patient population: The final protocol for study 22240 stated that 240 patients were planned for enrollment to ensure 216 evaluable patients (72 in each of the three treatment groups). The completed study randomized a total of 277 patients, with 275 receiving study treatment. The study treated 83 patients in the new r-hFSH group and 94 in the approved Gonal-f® group, the two treatment groups pertinent to the primary efficacy objective of study 22240. These patients were enrolled from 26 US sites and 10 sites in Argentina.

The contribution from each site to treatment cycle one in study 22240 varied from 0.4% (Centers 054, 415, and 456 with one treated patient) to 6.5% (Center 406 with sixteen treated patients)

Duration of clinical trial: The patients could be treated for a maximum of three treatment cycles.

Inclusion criteria (reflecting the changes noted in Protocol Amendment #1):

1. Was an infertile woman wishing to conceive whose physician had recommended that she undergo ovulation induction (Note: The patient had documented at least a 12-month period during which she failed to conceive despite unprotected intercourse or repeated intrauterine insemination procedures).
2. Was premenopausal and aged 18 through 39 years, inclusive.
3. Was anovulatory or oligoovulatory (Note: Anovulation was presumed if the patient's usual cycle length was $\geq$ 41 days; if the usual cycle length was <41 days, anovulation was to be confirmed by serum progesterone measurement).
4. Had spontaneous menses or a positive response to progestin withdrawal within 6 months of study entry (start of treatment) (Note: Positive response to clomiphene citrate withdrawal one to six months prior to study entry was to be considered acceptable to demonstrate induced menses).
5. Had a male partner with a semen analysis within 6 months prior to study entry which was considered acceptable, according to the standard practice at the clinic, for ovulation induction (use of donor sperm was acceptable).
6. Had a body mass index (BMI) less than 35.0 kg/m^2.
7. Had patency and apparent normality of at least one fallopian tube with an ipsilateral functional ovary, as documented by an hysterosonogram or hysterosalpingography (HSG) within 3 years prior to study entry (Note: Patients with a single ovary were to be considered acceptable provided they met this criterion).
8. Was willing and able to comply with the protocol for the duration of the study.

Inclusion criteria (continued):

9. Had given written informed consent prior to any study-related procedure not part of normal medical care, with the understanding that the patient could have withdrawn consent at any time without prejudice to their future medical care.
10. Had laboratory screening results demonstrating:

    •Dehydroepiandrosterone sulfate (DHEA-S) <700 mcg/dL
    •Testosterone <200 ng/dL
    •FSH within normal limits
    •Glucose level within normal limits
    •Insulin level <25 μU/mL

Exclusion criteria:

1. Had a clinically significant systemic disease (e.g., insulin-dependent diabetes, epilepsy, severe migraine, intermittent porphyria hepatic, renal or cardiovascular disease, severe corticoid-dependent asthma) or clinically significant abnormal hematology, chemistry or urinalysis results at screening (Note: it was mandatory to exclude patients with an elevated fasting glucose level [>110 mg/dL] or fasting insulin level [>25 mcU/mL]).
2. Was known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B or C virus.
3. Had prior severe OHSS or significant allergic response to urinary gonadotropin preparations.
4. Had any medical condition which, in the judgment of the investigator and/or sponsor, may have interfered with the absorption, distribution, metabolism or excretion of the study drug.
5. Had an ongoing pregnancy, any pregnancy within 3 months prior to study entry, or any contraindication to pregnancy or carrying pregnancy to term.
6. Had clinically significant abnormal findings evident on a transvaginal pelvic ultrasound performed within 2 cycles (maximum 90 days) of study entry.
7. Had poor response in a prior gonadotropin stimulation cycle, defined as an estradiol level <100 pg/mL per mature follicle (≥16 mm mean diameter).
8. Had prior excessive response to gonadotropin stimulation as defined by development of >3 mature follicles at a treatment dose of 75 IU.
9. Received treatment with gonadotropins, clomiphene citrate or gonadotropin releasing hormone (GnRH) analogs within one month prior to study entry (Note: use of oral contraceptive pills or progestin was allowed up to the start of the treatment cycle).
10. Had hypothyroidism (untreated) (Note: Patients with low TSH levels who were receiving replacement therapy [e.g., Synthroid®] could be enrolled at the discretion of the investigator if local laboratory results demonstrated satisfactory thyroid function).
11. Had hyperprolactinemia (untreated).

Exclusion criteria (continued):

12. Had adrenal congenital hyperplasia, partial or complete enzymatic block.
13. Had abnormal, undiagnosed, gynecological bleeding.
14. Had known current American Society of Reproductive Medicine (ASRM) stage III or IV endometriosis.
15. Had a residual ovarian cyst with a mean diameter >25 mm or an E2 >100 pg/mL at the baseline examination.
16. Had three or more consecutive unsuccessful gonadotropin cycles.
17. Had three or more consecutive pregnancy losses, due to any cause.
18. Had insulin resistant PCO (untreated) Note: Patients with insulin resistance who were receiving insulin-sensitizing agents (e.g., metformin, Avandia®) could be enrolled at the discretion of the investigator if the screening laboratory results indicated normal glucose/insulin levels.
19. Was simultaneously participating (within 3 months prior to study entry) in another investigational drug or device trial.

Reviewer's comment on the inclusion/exclusion criteria: The protocol and protocol amendment #1 represented a significant departure from previous studies for gonadotropin approval that defined the anovulatory study population in terms of resistance to clomiphene citrate treatment. In this reviewer's opinion, by eliminating this requirement of clomiphene resistance from the study and allowing the use of insulin-sensitizing agents, the sponsor has changed the patient population that was analyzed as anovulatory.

Therefore, the ovulation and pregnancy rates in this study would not be comparable to previous clinical studies of anovulatory patients. Furthermore, the differences in the anovulatory patient population studied should be reflected in the label of the new r-hFSH formulation.

Trial period: For March 2001 through July 2002.

Dosage and administration: Patients were screened within three days after menses onset (natural or induced) using ultrasound and a blood sample. Patients were randomized to: the new formulation of Gonal-f® (r-hFSH), the approved Gonal-f® formulation or Fertinex® (a urinary-derived follitropin). The protocol for dose initiation and adjustment was:

- Patients in the r-hFSH formulation treatment arm-- For cycle 1, the starting dose was 5.5 mcg per day sc, could be increased by the investigator to 8.3 mcg on treatment day 14 if no significant ovarian response. An additional increase to 11 mcg per day on treatment day 21 was allowed if no substantial ovarian response. The investigator could decrease the dose to a minimum of 2.8 mcg daily, at any time. Treatment duration was $\leq$ 28 days per cycle, with a maximum of 3 cycles per patient.

Dose initiation and adjustment (continued):

- Patients in the approved Gonal-f® formulation treatment arm – For cycle 1; the starting dose was 75 IU sc daily. If no significant ovarian response was seen by treatment day 14, the dose was increased to 112.5 IU. An additional increase of 37.5 IU to 150 IU could be made by the investigator on day 21 provided there was no significant ovarian response. The investigator could decrease the dosage to a minimum of 37.5 IU daily at any time. Treatment duration was ≤ 28 days, except in cases of imminent ovarian response.

- Patients in the Fertinex® arm – For cycle 1; the starting dose was 75 IU sc daily. If no significant ovarian response was seen by treatment day 14, the dose was increased to 112.5 IU. An additional increase of 37.5 IU to 150 IU could be made by the investigator on day 21 provided there was no significant ovarian response. The investigator could decrease the dosage to a minimum of 37.5 IU daily at any time. Treatment duration was ≤ 28 days, except in cases of imminent ovarian response.

Reviewer's comment: The sponsor originally stated that the new Gonal-f® formulation (r-hFSH) was originally identified as micrograms (mcg) of protein per vial and that designation has been changed to 5.5 mcg of protein per vial [to be considered equivalent to 75 IU of the approved Gonal-f® formulation]. The sponsor states that the change in equivalence in terms of micrograms more accurately reflect the conversion factor and delivered dose.

In this reviewer's opinion, the clinical impact of this mcg dose difference in r-hFSH per vial across the two studies is unknown. The difference in mcg of protein per vial is an approximate difference. However, this difference is considered an acceptable deviation in a fill of a given ampule as discussed with the Chemistry Reviewer. Therefore, although patients in study 21884 received a lower protein dose per vial, this may not be clinically significant since lots can vary by

Treatment protocol: Patients began between cycle days 3 to 5 (Patients with a baseline serum estradiol of greater than 100 pg/mL were not started, but given a rest cycle. If the patient did not begin treatment in the cycle immediately following the rest cycle, she was discontinued from treatment. Patient visit intervals for ultrasound and estradiol monitoring depended on individual patient response.

Recombinant human chorionic gonadotropin (Ovidrel®) in a single 250 mcg injection was administered when the following criteria were met:

1) at least one follicle (but no more than three) reached a mean diameter of ≥ 17 mm
2) serum estradiol levels were within an acceptable range for the numbers of follicles present (approximately 150 pg/mL per mature follicle).

Insemination was to occur via intercourse or intrauterine insemination within 48 hours following Ovidrel® administration. A pregnancy test was to be performed between days 15 and 18 post-hCG. Patients with negative pregnancy tests or cycles that were discontinued (other than for OHSS) could then undergo additional stimulation cycles to a maximum of three cycles.

Reviewer's comments:

1. **Study 22240 used a subcutaneously administered recombinant human chorionic gonadotropin (Ovidrel®) as compared to study 21884 that used an intramuscularly administered urinary-derived human chorionic gonadotropin (Profasi®). It is unknown whether there would be a change in the study outcome had both studies used the same route and type of human chorionic gonadotropin.**
2. **The sponsor reports that serum hCG levels of > 10 mIU/mL were considered as a positive pregnancy test, regardless of the local lab interpretation. In this reviewer's opinion, it is not acceptable to reinterpret serum hCG levels without re-evaluating the sample at a central laboratory for confirmation of the actual value.**

Demographic and baseline characteristics:

Efficacy of the new r-hFSH was assessed by comparison to the approved Gonal-f® treatment group. These two treatment groups were similar with respect to most baseline characteristics for the new Gonal-f® formulation (r-hFSH) arm and the approved Gonal-f® treatment arm. Demographic characteristics for the r-hFSH treatment group and the approved Gonal-f® treatment group are seen in Appendix 2 – Table 1B.

Demographic information for study 22240 included the following parameters:

- Mean patient age was 30 years (29.3 mean patient age in the r-hFSH formulation and 30.7 mean patient age in the approved Gonal-f® formulation).
- Mean weight was 72 kg in both the r-hFSH formulation arm and the approved Gonal-f® arm.

Demographic information (continued):

- Body Mass Index (BMI) was 26 kg/m2 in the r-hFSH treatment arm and the approved Gonal-f® treatment arm.
- The racial profile for study 22240 was similar in the r-hFSH treatment arm and the approved Gonal-f® treatment arm.

Other key baseline characteristics for the r-hFSH group and the approved Gonal-f® group are seen in Appendix 2 – Table 2B and 3B.

- Current smoking was reported by 4 of 83 patients (4.8%) using the r-hFSH formulation and 11 of 94 patients (11.7%) in the approved Gonal-f® formulation group, although the difference was not statistically significant.
- Characteristics including previous pregnancies, previous ectopic pregnancies, previous therapy for infertility and duration of infertility were not statistically significant between the two groups.
- Screening serum hormonal parameters (FSH and estradiol) did not demonstrate statistically significantly difference between the two formulation groups.

Reviewer's comments on the baseline and demographic characteristics noted in study 22240:

1. **The only statistically significant difference seen between the new r-hFSH formulation group and Gonal-f® group was the mean age of patients. However, although the mean age difference was statistically significant, it is less than a 1 year difference, it is probably not clinically meaningful. (See Appendix 2 - Table 1B)**
2. **The r-hFSH group had fewer current smokers than in the approved Gonal-f® formulation (See Appendix 2 - Table 2B), although this difference was not statistically significant. It is unknown if differences in smoking habits could have a negative impact on ovulation. Other parameters of smoking habits (such as previous smoking - documented in 11.4% of the new r-hFSH group and 12% of the approved Gonal-f® group) were similar when comparing treatment groups.**
3. **The r-hFSH group had mean duration of infertility of 6 months longer than the approved Gonal-f® group, although this difference was not statistically significant. It is unknown if this increased duration of infertility had a negative impact on patients treated in the r-hFSH group.**
4. **All treatment groups had identical semen analysis results, all were "acceptable". It is unknown whether study centers used the same methods or guidelines for semen analysis. Therefore, it is unknown if the different sperm analysis interpretations had an impact on ovulation rates.**

Primary efficacy assessment for study 22240:

The primary efficacy endpoint for study 22240 was ovulation rate. The sponsor defined the ovulation rate as the number of patients who ovulated (mid-luteal progesterone $\geq$ 10 ng/mL) divided by the total number of patients. The sponsor noted that ovulation was assumed to have occurred in any patient who became pregnant even if the progesterone level was below the criteria of 10 ng/mL or missing. The original protocol stated that the difference in ovulation rates between the r-hFSH formulation and the approved Gonal-f® formulation would be calculated using a 97.5% two-sided confidence interval.

Equivalence between the new and approved Gonal-f® formulations would be declared if the confidence interval was between (-20% and 20%) inclusive.

Amendment 2 (dated 22 October 2001) revised the statistical analysis plan for 22240 and changed the confidence interval test for the difference in ovulation rates to a 95% one-sided lower confidence. This change occurred seven months after the first site initiated treatment. The sponsor stated that "the new Gonal-f® formulation (r-hFSH) would be declared non-inferior to the approved Gonal-f® formulation in the first cycle of treatment if the lower limit of the confidence bound were greater than -20%".

Reviewer's comments:

1. **Protocol Amendments 1 and 2 were not submitted to the Agency and therefore, not reviewed by the Division.**
2. **The original statistical analysis plan for study 22240 stated that a 97.5% two-sided confidence interval of the first treatment cycle of the difference in ovulation rates between the r-hFSH and Gonal-f® treatment group that was stated in their original protocol was used.**
3. **The sponsor performed an interim efficacy analysis of the ovulation rate after the first treatment cycle, and this was not planned in the protocol for study 22240. However, for the purposes of an efficacy analysis, the Division will only consider the first treatment cycle.**
4. **The sponsor included an urofollitropin group (Fertinex® [u-hFSH]) in study 22240. However, only first cycle data from r-hFSH and the approved Gonal-f® treatments (as stated in the primary efficacy objective of study 22240) will determine clinical non-inferiority of r-hFSH.**

The sponsor designated multiple secondary efficacy endpoints including:

- Cumulative ovulation rate and ovulation rates for cycles 2 and 3
- Number of vials and amount of FSH used
- Duration of FSH treatment
- FSH dosing and treatment outcome
- Number of follicles $\geq$ 17 mm and $\geq$ 15 mm on the day of hCG in each cycle and over cycles
- Serum estradiol levels in each cycle
- Endometrial thickness (mm) on the day of hCG in each cycle
- Mid-luteal progesterone level (ng/mL) in each cycle
- Cycle cancellation rate
- Total, biochemical, ectopic and clinical pregnancy rate

Protocol violations and other allocation issues:

Total allocation: Study 22240 enrolled and randomized 277 patients, with 2 patients discontinuing prior to receiving any gonadotropins after deciding not to participate. Two hundred seventy-five patients were treated with study medication in the three treatment groups (r-hFSH, the approved Gonal-f® or Fertinex®)

Primary efficacy analysis included: 177 total patients that received at least one dose of either r-hFSH or the approved Gonal-f® formulation.

Of note in these two treatment arms:

- 153 patients (86.4%) received hCG administration
- 1 patient was administered hCG without having progesterone measurements. This patient had refused to have blood samples taken, and the sponsor reported that this patient was excluded from the evaluable analysis.

The most common reasons for protocol violations in patients in the two efficacy treatment groups in study 22240 included:

- non-compliance with gonadotropin dosing (5 patients)
- deviation in entrance criteria (5 patients)
- taking concomitant medications that could interfere with ovulation (4 patients)

The distribution of these excluded patients in the two efficacy treatment groups is seen in Appendix 2 - Table 4B.

Reviewer's comments:

Overall, failure to meet hCG administration criteria is was the most frequent protocol deviation, but the sponsor stated that this was not a reason for exclusion from analysis.

Reviewer's comments (continued):

The sponsor noted that 7 patients failed to meet the hCG criteria in treatment cycle 1 (2 subjects in the r-hFSH and 5 subjects in the approved Gonal-f® group) but were included in the final analysis. This reviewer agrees with the sponsor's inclusion of those treated patients in the final outcome. In addition, in this reviewer's opinion, the numbers of patients that had protocol violations or deviations (for any reason) resulted in a minimal impact on the overall efficacy analysis, and appeared to be equally distributed.

Primary efficacy analysis:

The sponsor's designated primary efficacy endpoint was ovulation. In order to compare the ovulation rate between groups, the intent-to-treat population was evaluated. The efficacy analysis for the treated patient population is seen in Appendix 2 - Table 5B.

The sponsor's primary efficacy endpoint demonstrated:

a. The ovulation rate (as defined by a progesterone level of $\geq$ 10 ng/mL) for the first treatment cycle was:

- 71% (59 of 83 patients ovulated) when treated with the new Gonal-f® (r-hFSH) formulation
- 68% (64 of 94 patients ovulated) in the approved Gonal-f® formulation.

b. Patients who completed treatment and received hCG was an additional key secondary efficacy parameter. For the evaluable group in the first treatment cycle:

- 74 of 84 patients (88%) completed treatment using the r-hFSH formulation
- 79 of 94 patients (84%) completed treatment using the approved Gonal-f® formulation.

Reviewer's comments:

- **The primary efficacy parameter (ovulation rate) for the r-hFSH formulation is non-inferior to the ovulation rate seen in subjects who were treated with the approved Gonal-f® formulation. In addition, secondary analysis of mid-luteal progesterone level or rate of completion of treatment (as measured by administration of hCG) did not appear to be clinically different between the two groups. (See Appendix 2 - Table 5B)**

Reviewer's comments (continued):

- **The clinical pregnancy rate for the first treatment cycle was slightly higher in the r-hFSH formulation compared to the approved Gonal-f® formulation although this was not statistically significant (see Appendix 2 - Table 5B).**
- **One patient was involved in a randomization problem at one site (Center 383). There was a problem in the phone system that caused the patient to have a different treatment number than would the phone system had been working. This one case does not appear to indicate that there were major problems with the sponsor's randomization process.**

In this reviewer's opinion, the r-hFSH group appears to be non-inferior to the approved Gonal-f® group on the primary efficacy outcome measure.

Pregnancy rates as calculated using the first treatment cycle was an important secondary efficacy parameters is seen in Appendix 2- Table 6B. The sponsor defined the clinical pregnancy rate as the number of patients with one or more fetal sacs – with or without a fetal heartbeat.

Reviewer's comment: The Division recommends that the definition of a clinical pregnancy should be a fetal sac with a heartbeat.

Study 22240 had a clinical pregnancy rate of approximately 20% in the two evaluable patients groups treated with r-hFSH or the approved Gonal-f®. This clinical pregnancy rate is consistent with the clinical pregnancy rate seen in a recent ovulation induction study. [14]

The clinical pregnancy data for the first treatment cycle is seen in Appendix 2 – Table 6B:

- 23 clinical pregnancies (27.7%) in the r-hFSH formulation group
- 18 clinical pregnancies (19.1%) in the approved Gonal-f® formulation group

The clinical livebirth data for the first treatment cycle is seen in Appendix 2 – Table 6B:

- 22 livebirths (26.5%) in the r-hFSH formulation group
- 17 livebirths (18.1%) in the approved Gonal-f® formulation group

Reviewer's comments: Study 22240 was not powered to detect a difference in clinical or livebirth pregnancy rates. However, it is reassuring that no difference was noted between the r-hFSH group and the approved Gonal-f® groups.

Treatment exposure to FSH is seen in Appendix 2 - Table 7B. The sponsor measured the exposure to the approved Gonal-f® and new Gonal-f® formulation (r-hFSH) formulations using the following:

Results for Treatment Exposure

	r-hFSH group	Gonal-f® group
Mean number of ampules (total)	14.4	19.0
Mean duration of treatment (days)	13.0	16.2

Source: Appendix 2 - Tables 7B.

Reviewer's comment: There is a decreased amount of vials and duration of treatment in the r-hFSH formulation arm compared to the approved Gonal-f® formulation (both p<0.005). This is consistent with the shorter treatment duration and smaller dose differences for r-hFSH seen in study 21884. The reason for this decreased dose and duration of treatment is unknown.

D. Efficacy Conclusions

This reviewer concludes that:

- Study 21884 demonstrates that the new Gonal-f® (r-hFSH) formulation is non-inferior to Fertinex® for the primary efficacy endpoint – the number of fertilized oocytes.
- In addition, Study 21884 demonstrates no significant difference in the secondary efficacy endpoints for numbers of total oocytes retrieved, metaphase II oocytes retrieved, or embryos between the new Gonal-f® (r-hFSH) and Fertinex® formulations.
- Study 22240 demonstrates that the new Gonal-f® (r-hFSH) is clinically non-inferior to the approved Gonal-f® formulations for the primary efficacy endpoint - ovulation rate.

These two supportive clinical studies (21884 and 22240) provide adequate documentation of efficacy upon which approval of the new r-hFSH formulation can be based. In addition, the efficacy outcome of clinical pregnancy does not appear to change with use of the new r-hFSH formulation in the two submitted clinical studies.

VII. Integrated Review of Safety

A. Brief statement of conclusions

The original safety database for the approved Gonal-f® formulation was derived from four clinical trials previously reviewed in NDA 20-378. The safety profile for the new Gonal-f® formulation (r-hFSH) obtained from studies 21884 and 22240 appears to be similar to previous safety profiles in the original clinical studies using the approved Gonal-f® formulation. The serious adverse events with gonadotropin use (ovarian hyperstimulation syndrome and multiple births) for the new r-hFSH formulation appear to be equivalent to the approved Gonal-f® formulation, and additionally to an urofollitropin (Fertinex®).

B. Description of Patient Exposure

Patient exposure for the approved Gonal-f® product has been ongoing since 1997, and is adequate. The patient exposure for the new r-hFSH formulation was limited to the two clinical trials (A total of 320 patients exposed to the new r-hFSH formulation in the two studies [21884 and 22240] that were submitted). However, since the safety of the r-hFSH formulation appears to be similar to the current approved Gonal-f® formulation, this exposure is adequate.

C. Methods and Specific Findings of Safety Review

The safety profile of the approved Gonal-f® formulation is based primarily on data from the studies previously reviewed in NDA 20-378 (Please see the Original Medical Officer's Review of Gonal-f® was March 3, 1994, Medical Officer's Original Summaries of Amendment Dated April 18, 1996, November 26, 1996, and February 13, 1997, Medical Officer's Review of Safety Update Dated July 17, 1997).

The final review of the safety data for the approved Gonal-f® formulation concluded that the approved Gonal-f® formulation was as safe as a comparable urinary-derived gonadotropin. [See Medical Officer's original review of Gonal-f® (NDA 20-378) dated September 13, 1994, Medical Officer's Summary of NDA 20-378 Amendment dated January 15, 1997, Medical Officer's Summary of Information Amendment dated February 13, 1997 and a safety update from July 17, 1997.].

The safety profile for the new r-hFSH formulation is based on safety data from 986 total subjects treated in the two supportive clinical studies (21884 and 22240).

Reviewer's comments:

1. **The safety profile for the new r-hFSH formulation was compared with the other two treatments [the approved Gonal-f® formulation and a urofollitropin (Fertinex®)] in the two clinical studies (21884 and 22240).**
2. **In addition, a comparison of the safety profile for the new r-hFSH formulation (from the two supportive clinical studies - 21884 and 22240) to previous clinical studies for the approved Gonal-f® product (NDA 20-378) was performed for historical interest.**

Study 21884:

Patients undergoing assisted reproductive technology (*in vitro* fertilization and intracytoplasmic injection):

Patient Disposition/Treatment: The evaluable group assessed for safety included 711 subjects who were enrolled and treated with gonadotropins. Adverse events were coded using the WHO Adverse Event Reaction Terminology Dictionary, and the severity of adverse events was graded by the sponsor using a modified WHO criteria.

The safety assessments reported by the sponsor included:

1. Overall adverse events
2. Serious adverse events
3. Ovarian hyperstimulation syndrome
4. Safety data
5. Local tolerance at injection sites
6. Study termination rate
7. Multiple pregnancy rate

1. Overall adverse events:

The overall adverse events were examined for all three treatments groups for study 21884. In the treated patient population, 441 of 711 patients (62%) reported adverse events (See Appendix 3 – Table 1A).

In each of the treatment groups, the number of patients with adverse events included:

- 145 patients (61.2%) in the new r-hFSH group
- 153 patients (64.6%) in the approved Gonal-f® group
- 143 patients (60.3%) in the Fertinex® group.

The most frequently reported adverse events in all treatment groups combined were abdominal pain (24%), headache (18%) and enlarged abdomen (13.9%).

The two most common adverse events were abdominal pain and headache. Abdominal pain and headaches have been noted to occur with use of the currently approved Gonal-f® formulation (See NDA 20-378).

a. Abdominal pain was the most common reported adverse event.

- 55 reported patients (23.2%) in the new formulation of r-hFSH group
- 62 reported patients (23.2%) in the approved Gonal-f® group
- 56 reported patients (23.2%) in the Fertinex® group

  - Abdominal pain can also be the result of the egg retrieval process. Elimination of the patients that complained of pain after retrieval did not demonstrate significant differences between the treatment groups.

b. Headache was the second most common reported adverse event. The proportion of patients with headaches in the three treatment groups included:

- 44 reported patients (18.6%) in the new r-hFSH group
- 51 reported patients (21.5%) in the approved Gonal-f® group
- 33 reported patients (13.9%) in the Fertinex® group

  - In comparison to headaches, the number of patients with migraines was clinically different across the formulations. Four patients had migraines in the new r-hFSH group, and none were reported in the approved Gonal-f® or Fertinex® groups.

Reviewer's comments: The overall rates of adverse events in the r-hFSH formulation group were similar to rates seen in the approved Gonal-f® and Fertinex® groups. (See Appendix 3 – Table 1A)

- **There was more abdominal pain reported in the r-hFSH group than the other two formulation groups. It is unknown whether this is related to the actual oocyte retrieval process (differences in anesthesia, differences in retrieval procedures) or directly related to the new r-hFSH formulation.**
- **The rates of headaches across the treatment groups were clinically equivalent across the treatment groups, although somewhat higher than a previously completed comparable study (5533) with the approved Gonal-f® (12.5%). (See Appendix 3 – Table 2A) However, it is important to note that the number of patients with headaches seen in the r-hFSH group is similar to the other two treatment groups.**

Reviewer's comments (continued):

- **The rate of migraines was somewhat higher in the r-hFSH group (4 events (1.7%) compared to 0%). However, two of these migraine events appeared to be associated with Lupron®). These other drugs (anesthesia, gonadotropin-releasing hormone agonists, progesterone for luteal support) may also increase the rate of headaches and migraines observed, and therefore, confound whether r-hFSH formulation is responsible for the migraine/headache. The number of migraine events observed is too small to determine if r-hFSH has an increased risk of causing a migraine compared to other gonadotropins. Therefore, in this reviewer's opinion, the label should reflect the rate of headaches and migraines seen in the r-hFSH group in this study.**

2. Serious adverse events:

There were no deaths or thromboembolic phenomenon seen in study 21884. Twenty-six patients (3.7%) had serious adverse events were reported:

- The new Gonal-f® formulation (r-hFSH) group: 3 ectopic pregnancies, 1 appendicitis, 1 ovarian hyperstimulation syndrome, 1 fetal death, 1 missed abortion, 1 fetal congenital anomaly (Down's syndrome by amniocentesis), and 1 fetal maturation impaired (acrania).
- The approved Gonal-f® group: 3 ovarian hyperstimulation syndrome, 3 fetal deaths, 3 ectopic pregnancies and 1 second trimester abortion.
- The Fertinex® group: 2 ectopic pregnancies, 1 ovarian hyperstimulation syndrome, 1 molar pregnancy, one placental disorder (placental detachment) and one patient with dehydration (hyperemesis gravidarum).

Reviewer's comments:

1. **The overall serious adverse event rates appear to be roughly equivalent when comparing the three gonadotropin treatment groups (i.e. the new r-hFSH formulation, the approved Gonal-f® formulation and the Fertinex® formulation groups.**
2. **The new r-hFSH formulation does not appear to demonstrate increases in the number of patients with ectopic pregnancies or abortions. These complications of pregnancy are well recognized complications associated with gonadotropin use. In conclusion, the safety profile for serious adverse events does not show new trends or additional safety concerns.**

3. Ovarian hyperstimulation syndrome:

The overall rate for ovarian hyperstimulation syndrome was reported as an adverse event in 37 patients (5.2%)

Ovarian hyperstimulation was reported by treatment group in:

- 11 patients (4.6%) using the new r-hFSH formulation
- 13 patients (5.5%) in the approved Gonal-f® formulation
- 13 patients (5.5%)in the Fertinex® group

Severe ovarian hyperstimulation was reported in one patient (0.4%) in the new r-hFSH formulation group, one in the Fertinex® group and three patients (1.2%) in the approved Gonal-f® formulation group.

Reviewer's comments:

1. **The overall rate of ovarian hyperstimulation syndrome of 4.6% (11 patients) for the new r-hFSH group is similar (and somewhat lower) than the 5.5% (13 patients) seen in the approved Gonal-f® and Fertinex® groups. However, Study 21884 was not powered to demonstrate a difference in ovarian hyperstimulation syndrome rates, and the differences between the groups do not appear to be clinically significant.**
2. **The sponsor's reported rate of severe ovarian hyperstimulation syndrome occurred in 0.04% of patients in the r-hFSH formulation, lower than the rate in the approved Gonal-f® formulation. However, since there were no uniform criteria for the classification of ovarian hyperstimulation syndrome, the rate of severe could have been under-reported. This reviewer noted that 7 patients had serum estradiol levels over 6,000 pg/mL during gonadotropin stimulation, 2 of the 7 had serum estradiol levels over 9,000 pg/mL. Technically, any patient with serum estradiol levels of over 6,000 pg/mL of serum estradiol during gonadotropin stimulation is at a very high risk of being diagnosed with severe hyperstimulation.[15] Of these seven patients with serum estradiol levels (during gonadotropin stimulation) of over 6,000 pg/mL, only three were listed as having ovarian hyperstimulation, and none were listed as having severe ovarian hyperstimulation (although by use of a modified classification of ovarian hyperstimulation syndrome that includes serum estradiol criteria, all four subjects could have potentially been reclassified as severe, depending other findings at the time of evaluation).**
3. **One patient (031-0017) had a serum estradiol on day of hCG administration of 11,500 pg/mL (in the r-hFSH group). This patient had abdominal pain, distention, nausea and vomiting after hCG administration and was listed as having moderate ovarian hyperstimulation syndrome. The protocol for study 21884 did not specify a classification system for ovarian hyperstimulation syndrome, and each individual investigator was responsible for classifying the severity of ovarian hyperstimulation syndrome as an adverse event.**

Reviewer's comments (continued):

4. **This Argentinian patient with an estradiol of 11,500 pg/mL was classified as moderate hyperstimulation, whereas this reviewer suspects that if this patient had been in the United States she would have been classified as severe. In this reviewer's opinion, this patient should have been reclassified as severe ovarian hyperstimulation.**
5. **There were seven patients identified with significantly elevated estradiol levels, but none were diagnosed as having severe ovarian hyperstimulation. This may have resulted because of differences in measurement of serum estradiol at the local laboratories assays or different practice patterns of determining when a patient should have her cycle cancelled.**
6. **This reviewer concludes that there appeared to be slight differences between the centers in the determination of the severity of ovarian hyperstimulation syndrome. This reviewer recommends that if the sponsor is going to perform multinational studies that a classification system for ovarian hyperstimulation should be included in the protocol for uniformity. This reviewer also recognizes that elevated serum estradiol values alone are inadequate to classify the severity of ovarian hyperstimulation syndrome, and will not reclassify patients based on this value alone.**
7. **This reviewer also acknowledges that, (in the worst case scenario), even if all patients with serum estradiol levels over 6,000 pg/mL in the r-hFSH group at the end of the stimulation period were reclassified as having severe ovarian hyperstimulation, the rate of severe ovarian hyperstimulation syndrome for new r-hFSH formulation group (5 total patients or 5 total patients or 2% of ITT population) would still be approximately equivalent to the rate of severe ovarian hyperstimulation seen in the approved Gonal-f® group (2% of the ITT population).**

4. Laboratory safety data:

Patients were evaluated for clinical laboratory parameters (hematology and blood chemistry) at baseline (pre-study) and post-treatment (post-hCG Day 15-18). Two central laboratories were used for the analysis of blood samples collected during the study:

- [redacted], performed hematology, chemistry and screening endocrine assessments on patients enrolled at US trial sites.
- [redacted], performed hematology, chemistry and screening endocrine assessments on patients enrolled at the Argentinian trial centers.

Reviewer's comment: The results of the hematology and chemistry laboratories are presented separately for each central laboratory (Appendix 3 – Table 3A for Argentina and Table 4A for the United States).

a. Hematology:

The normal ranges were slightly different at the two central laboratories [Argentina] and [United States]) for routine hematology parameters including: hematocrit, neutrophils and white blood cell count. No clinically significant differences in mean hemoglobin, hematocrit or white blood cell count at the (U.S.) or Argentina) were seen between the treatment groups at baseline or post-treatment levels (See Appendix 3 – Tables 3B and 4B).

- For neutrophils, a mean decrease of 2.3% was seen after administration of r-hFSH as compared to an increase of 0.9% and 1.9% in the Fertinex® and Gonal-f® groups. This was not seen in the US laboratory data.

Reviewer's comment: The clinical significance of this mean decrease in neutrophil count between treatment groups is unclear. However, since this was not seen in the larger treatment group in the United States (approximately 453 subjects in the US compared to 155 subjects in Argentina). The mean decreased neutrophil count in the r-hFSH group in Argentina was not below the normal range for neutrophils for and therefore, is probably not a clinically significant treatment group trend.

Clinically significant individual hematology laboratories seen post-treatment:

- Hemoglobin and hematocrit – one patient in the approved Gonal-f® group (#020-0003) and one patient in the Fertinex® group (#023-0003) had low hemoglobin and hematocrit levels after treatment (11.9g/dL and 34% and 10.8g/dL and 30.3%). Neither patient had a critically low value noted.
- White blood cell count – two patients in the approved Gonal-f® group (#014-0021 and #023-0012) and one patient in the new r-hFSH group (#014-0002) had an elevated white blood cell count after treatment.
- Neutrophils – no clinically significant abnormalities were noted.

Reviewer's comments:

1. **It is expected that there will be a downward trend in hemoglobin and hematocrit in patients that undergo procedures during assisted reproductive technology (ART) therapy. The downward trend in these red blood cell indices reflects an anticipated blood loss of approximately 200 cc post-ART procedure[16].**
2. **In this reviewer's opinion, the fact that less than 1% of the total patient population had significant decreases in red blood cell indices represent individual variations post ART procedure, and not as a result of overall gonadotropin therapy.**
3. **No clinically significant changes from baseline to post-treatment were seen in any of the three treatment groups, and there did not appear to be clinically significant trends that occurred when comparing the three treatment groups.**
4. **Hemoglobin and hematocrit fell slightly from pre-study to post-study in the United States, but not in Argentina. (See Appendix 3 – Tables 3B and 4B) The reason for this decrease in hemoglobin and hematocrit is probably a result of the oocyte retrieval process. However, the reason why this was not seen in Argentina is unknown.**
5. **Mean white blood cell count and neutrophil levels increased from baseline to post-treatment in all three treatment groups. (See Appendix 3 – Tables 3B and 4B)This upward trend occurred in all treatment groups in both countries. The clinical significance of this trend is unknown, but is probably related to the oocyte retrieval and transfer process. In this reviewer's opinion, the new r-hFSH treatment does not appear to cause unexpected trends in hematology parameters.**
6. **The small number of subjects (4) with clinically significant hematology parameters does not be specifically related to the new r-hFSH treatment group. In addition, all three patients with elevated white blood cell counts post-treatment were pregnant.**

Therefore, in this reviewer's opinion, there were no obvious hematologic abnormalities or trends seen with the use of the new r-hFSH formulation.

b. Blood chemistry:

The normal ranges for chemistry values were slightly different at the two central laboratories — [Argentina] and — [United States]) for routine chemistry parameters including: creatinine, AST, and blood urea. (See Appendix 3 – Table 4B) No clinically significant differences in mean creatinine, sodium, urea, AST or ALT levels at the — (U.S.) or — (Argentina) were seen between the treatment groups at baseline or post-treatment levels. (See Appendix 3 – Tables 3B and 4B)

Clinically significant individual chemistry laboratories seen post-treatment:

- Potassium – one patient in the Fertinex® group (#027-0004) had a potassium of 7.5 mmol/L post-treatment.
- Sodium – one patient in the approved Gonal-f® group (#023-0012) had a sodium of 130 mmol/L post-treatment.
- ALT and AST– five patients in study 21884 had abnormal elevations in liver function tests post-treatment. They included one patient (#014-0002) in the new r-hFSH group, one patient in the Gonal-f® group (#008-0004) and three patients in the Fertinex® group (#031-0031, #023-0003 and #021-0019).

Reviewer's comments:

1. **No clinically significant changes from baseline to post-treatment in chemistry laboratories were seen in the three treatment groups. (See Appendix 3 – Tables 3B and 4B). In addition, no significant differences in trends between the group laboratory values pre- and post-treatment were seen between the United States and Argentina.**
2. **The two patients with clinically significant abnormal chemistry abnormalities including the subject [#023-00012] with the abnormally decreased sodium level (who also had an abnormal calcium and urea level) and the subject [#027-0004]) with the abnormal potassium level both had reported ovarian hyperstimulation syndrome. Multiple chemistry abnormalities including elevated potassium levels and decreased sodium levels have been reported in patients with the diagnosis of ovarian hyperstimulation syndrome. Therefore, in this reviewer's opinion, the chemistry abnormalities were the result of the ovarian hyperstimulation and not the gonadotropin used.**
3. **Analysis of the five patients with clinically significant liver abnormalities (#008-0004, #014-0002, #021-0019, #023-0003 and #031-0031) shows that none had liver function tests greater than 3 times the upper limit of normal. Furthermore, these clinical abnormalities were seen sporadically in one patient in the approved Gonal-f® group, one patient in the r-hFSH group, and three patients in the Fertinex® group. (less than 1% of all three treatment groups). Therefore, no pattern of increased liver function testing was seen in the new r-hFSH arm, and the elevations may have been secondary to other factors. These factors may include: gonadotropin-releasing hormone agonist use, anesthesia use (some intravenous or other anesthesia is commonly used with oocyte retrieval) or ovarian hyperstimulation syndrome.**

Reviewer's comment (continued):

Therefore, in this reviewer's opinion, the new r-hFSH formulation did not appear to cause significant increases or unexpected trends in chemistry or liver function testing. The small number of subjects (7) with clinically significant chemistry parameters does not appear to indicate a trend in any treatment group.

c. Vital signs:

Systolic and diastolic blood pressure, pulse, and weight were recorded pre- and post-treatment for all three gonadotropin treatment groups. The most concerning change in vital signs with gonadotropin use is weight gain. Weight gain could represent an early sign of ovarian hyperstimulation syndrome (water retention).

The weight gain demonstrated by the patient from baseline to the completion of treatment included:

- 1.3 pound (lb) weight gain in the new Gonal-f® formulation (r-hFSH) treatment group
- 1.3 lb weight gain in the approved Gonal-f® formulation treatment group
- 1.8 lb weight gain in the Fertinex® treatment group

Reviewer's comments: No clinically significant differences in weight gain across the three treatment groups were noted. In this reviewer's opinion, a mean weight gain of less than 2 lbs is probably not clinically significant. A comparison of the three treatment groups (i.e. r-hFSH group, the approved Gonal-f® group and Fertinex® group), did not demonstrate clinically significant differences between treatment groups in measurements of systolic blood pressure, diastolic blood pressure, pulse or temperature.

5. Injection site disorders:

A total of 200 of 711 patients (28% of the treated patient population) experienced injection and/or application site disorders reported as adverse events during the treatment cycle. The most common injection site reaction seen (pain) occurred was reported as a severe adverse event in:

- 0 patients (0%) in the r-hFSH group
- 0 patients (0%) in the approved Gonal-f® group
- 2 patients (0.3%) in the Fertinex® group

Reviewer's comment: Injection site disorders appear to be similar across the three treatment groups. (See Appendix 3 – Table 3A). There is no evidence that the new r-hFSH formulation increases local tolerance reactions (as judged to be a severe adverse event).

6. Study termination for study 21884:

Treatment with the gonadotropins (the new r-hFSH formulation, the approved Gonal-f® formulation or Fertinex®) or human chorionic gonadotropin (hCG) were withheld for any of the following reasons (i.e. study termination):

- Failure to achieve pituitary desensitization
- Lack of ovarian response to FSH treatment
- An ovarian response to FSH treatment indicating an excessive risk of OHSS, according to the center's standard practice
- WHO grade 3 or 4 adverse event
- A complex of adverse events which, in the judgment of the investigator and subject to agreement with the sponsor, justifies treatment cessation

The major cancellation that results in a safety concern with gonadotropin use is cancellation of a treatment cycle because of an adverse event.

a. Patients that were cancelled for an adverse event included:

- 1 patient cancelled in the r-hFSH group (appendicitis)
- 1 patient cancelled in the approved Gonal-f® group (ectopic)

Reviewer's comment: No differences or trends in cycle cancellations for adverse events were noted across treatment groups.

7. Multiple birth rate/Miscarriage/Ectopic Rate:

a. The multiple birth rates in the two primary efficacy treatment groups. (See Appendix 2 – Table 15A).

- 16 patients had a twin birth (22.9%) and 4 (5.7%) had triplets in the new r-hFSH group
- 23 patients had a twin birth (27.7%) and 5 (6%) had triplets in the Fertinex® group

Multiple birth/miscarriage/ectopic rate (continued):

b. The miscarriage rate was reported (See Appendix 2 – Table 15A):

- 11 miscarriages (4.7%) in the r-hFSH formulation group
- 8 miscarriages (3.4%) in the Fertinex® group

c. The ectopic pregnancy rate was reported (See Appendix 2 – Table 15A):

- 3 patients (1.3%) in the r-hFSH formulation group
- 2 patients (0.8%) in the Fertinex® group

Reviewer's comments:

1. **The multiple birth rate for the new r-hFSH group was not statistically significantly different from the Fertinex® group (See Appendix 2 - Table 14A).**
2. **The numbers of miscarriages and ectopic pregnancies were compared between the two treatment groups. The difference between the miscarriage and ectopic pregnancy rates were not statistically different between treatment groups.**

In this reviewer's opinion, there do not appear to be clinical differences in multiple birth rate, miscarriages or ectopic pregnancies between the primary efficacy treatment groups. However, study 21884 was not powered to demonstrate clinical differences between these secondary endpoints.

Study 22240: Patients undergoing Ovulation Induction (OI)

Patient disposition/treatment: The evaluable group assessed for safety included 275 subjects who were enrolled and had at least one injection of study medication. Adverse events were coded using the WHO Adverse Event Reaction Terminology Dictionary.

The severity of adverse events was graded by the sponsor using a modified WHO criterion. The modified WHO criteria for severity of adverse events were graded using a four point scale (mild, moderate, severe and life-threatening). The safety assessments reported by the sponsor included:

1. Overall adverse events
2. Serious adverse events
3. Ovarian hyperstimulation syndrome
4. Safety data
5. Local tolerance at injection sites
6. Study termination rate
7. Multiple pregnancy rate

1. Overall adverse events:

The overall adverse events were examined for the three treatment groups in all three treatment cycles. In the treated patient population, (patients treated with at least one dose of gonadotropin), 174 of 275 total treated patients (63.3%) reported at least one adverse event during the study (see Appendix 3 - Table 1B).

In each of the treatment groups, the number of patients with adverse events included:

- 50 patients (60.2%) in the new r-hFSH group
- 62 patients (66%) in the approved Gonal-f® group
- 62 patients (63.3%) in the Fertinex® group

The most frequently reported adverse event in all treatment groups combined were headache (27.6%), abdominal pain (10.2%), and rhinitis (8.0%). The two most common adverse events were abdominal pain and headache. Abdominal pain and headaches have been noted to occur with use of the approved Gonal-f® formulation (See NDA 20-378).

a. Headache was the most common reported adverse event across all three treatment cycles. The proportion of patients with headaches in the three treatment groups included:

   - 22 patients (26.5%) in the r-hFSH group
   - 27 patients (28.7%) in the approved Gonal-f® group
   - 27 patients (27.6%) in the Fertinex® group

b. Abdominal pain was the second most common reported adverse event across all three treatment cycles.

   - 10 patients (12.0%) in the r-hFSH group
   - 6 patients (6.4%) in the approved Gonal-f® group
   - 12 patients (12.2%) in the Fertinex® group.

Reviewer's comments:

1. **Headaches were more common in the new r-hFSH group in this ovulation induction (OI) study [26.5%] (Appendix 3 – Table 1B) than the ART study [28.6%] (Appendix 3 – Table 1A). In addition, headaches in this r-hFSH group were more common than a similar OI study using a urinary-derived follitropin, Repronex® (5.6%).[14] However, the rate of headaches in the r-hFSH treatment is almost equivalent when compared to the other two treatment groups (i.e. the approved Gonal-f® formulation and Fertinex®) in study 22240. In addition, baseline headache rates in this OI study were not evaluated for the recruited patients.**

Reviewer's comments (continued):

2. **In this reviewer's opinion, headache rates seen with use of gonadotropins in study 22240 is unknown, but appears to be related to the recruited patient population, not gonadotropin treatment.**
3. **Other adverse events, including abdominal pain, breast pain, vaginal hemorrhage and ovarian cyst formation for the r-hFSH group were not significantly different from rates in the other two treatment groups [the approved Gonal-f® and Fertinex® formulation. (See Appendix 3 – Table 1B) or from a previous trial (5727) for the approved Gonal-f® formulation (See Appendix 3 – Table 2B).**

2. Serious adverse events:

There were no deaths or thromboembolic events in study 22240. There were 14 total serious adverse events reported (5.1%) for study 22240:

- The new r-hFSH group: 2 premature deliveries, 1 patient with a ruptured ectopic pregnancy, 1 patient with (moderate to severe) ovarian hyperstimulation, and 1 premature delivery of twins. (Note: One patient developed a positive HIV test during the study. Her husband had refused screening HIV testing, the sponsor listed this as a severe adverse event)
- The approved Gonal-f® group: 3 ectopic pregnancies, 1 spontaneous abortion, 1 clinical miscarriage and 1 patient with preeclampsia
- The Fertinex® group: 1 ectopic pregnancy and 1 ovarian torsion

Reviewer's comment: The serious adverse event rate appears to be roughly equivalent between the three gonadotropin treatment groups. The serious adverse event data in study 22240 does not demonstrate new trends or additional safety concerns.

3. Ovarian hyperstimulation syndrome:

The overall rate for ovarian hyperstimulation syndrome was reported as an adverse event in 18 patients (6.5%) Ovarian hyperstimulation was reported by treatment group in:

- 6 patients (4.6%) using the new r-hFSH formulation
- 6 patients (5.5%) in the approved Gonal-f® formulation
- 6 patients (5.5%)in the Fertinex® group

Serious ovarian hyperstimulation was reported in one patient (0.4%) in the new r-hFSH formulation group (#404-0003). No cases of severe ovarian hyperstimulation were reported in the r-hFSH, approved Gonal-f® or Fertinex® groups.

Reviewer's comments:

1. **The overall rate of ovarian hyperstimulation syndrome (OHSS) of 4.6% (6 patients) for the new r-hFSH group is similar than the rates seen in the approved Gonal-f® and Fertinex® groups. In addition, the overall rate of OHSS is similar to published rates a similar ovulation induction study[17].**
2. **The rate of severe OHSS seen in the r-hFSH group (1% of the r-hFSH patients treated) is similar to a previous ovulation induction trial for the approved Gonal-f® formulation (0.08%) [Submitted in study 5727 for NDA 20-378]. (See Appendix 3 – Table 2B). However, this patient was hospitalized and received albumin. In the opinion of this reviewer, patients that are hospitalized for OHSS should be considered severe OHSS.**
3. **In addition, no patients in study 22240 had serum estradiol levels during or post-treatment of greater than 6000 pg/mL.**

In the opinion of this reviewer, the rate of overall and severe ovarian hyperstimulation syndrome for ovulation induction patients provides additional evidence that the new r-hFSH formulation has an acceptable safety profile for ovarian hyperstimulation syndrome compared to the other two treatment groups (approved Gonal-f® and Fertinex®). However, this reviewer also notes that had there been a uniform classification of OHSS, these reported OHSS rates may have been higher.

4. Laboratory safety data:

Patients were evaluated for clinical laboratory parameters (hematology and blood chemistry) at baseline (pre-study) and post-treatment (post-hCG Day 15-18). Two central laboratories were used for the analysis of blood samples collected during the study. [redacted]) performed hematology, chemistry and screening endocrine assessments on patients enrolled at US trial sites.

[redacted] performed hematology, chemistry and screening endocrine assessments on patients enrolled at the Argentinian trial centers.

Reviewer's comments: The results of the hematology and chemistry laboratories are presented separately for each central laboratory (Appendix 3 – Table 3B for Argentina and Table 4B for the United States).

a. Hematology:

The normal ranges were slightly different at the two central laboratories ([redacted] [Argentina] and [redacted] [United States]) for routine hematology parameters including: hematocrit, neutrophils and white blood cell count.

Hematology (continued):
No clinically significant differences in mean hemoglobin, hematocrit, white blood cell count or neutrophil levels at the —— (U.S.) or (Argentina) were seen between the treatment groups at baseline or post-treatment levels for cycle 1 (See Appendix 3 – Tables 3B and 4B).

Clinically significant individual hematology laboratories (post-treatment):

- White blood cell count:
  - One patient (#356-0012) in the approved Gonal-f® group (Argentina) had a clinically elevated WBC count of 15 x 10^3/mcL in treatment cycle 2 (upper limit of normal was 11 x 10^3/mcL). This patient had two treatment cycles and was pregnant at the time the study termination laboratory was drawn.

Reviewer's comments:

1. **Hemoglobin and hematocrit fell slightly from pre-study to post-study in Argentina in all three treatment groups. The reason for this decrease in hemoglobin and hematocrit is unknown (See Appendix 3 – Table 3B).**
2. **Mean white blood cell count and neutrophil levels increased from baseline to post-treatment in cycle one in the three treatment groups. This upward trend occurred in all treatment groups in both countries. The clinical significance of this trend is unknown (See Appendix 3 – Table 3B)**
3. **Three patients had clinically abnormal platelet counts:**
   - **One patient (#525-0013) in the approved Gonal-f® group (U.S.) had a platelet count of 545 103/UL post-treatment cycle 1 (upper limit of normal 400 103/UL). This platelet count returned to normal in treatment cycle 2 to 372 103/UL**
   - **Two patients (#406-0012 and #452-0002 [both from the U.S.]) in the Fertinex® group had platelet counts of 488 and 463 103/UL at treatment termination.**

   These three patients with mildly elevated platelet counts all had chemical or ectopic pregnancies (patient #406-0012 had an ectopic pregnancy; patients #452-002 and #525-0013 had chemical pregnancies). In this reviewer's opinion, the elevated platelet counts could result from the abnormal pregnancy, and do not appear to be related to the gonadotropin treatment

Reviewer's comments (continued):
In this reviewer's opinion, the new r-hFSH treatment does not appear to cause unexpected trends in hematology parameters. In addition, the small number of subjects with clinically significant hematology parameters do not appear directly related to the new r-hFSH treatment group.

b. Blood chemistry:

The normal ranges for chemistry values were slightly different at the two central laboratories [Argentina] and [United States]) for routine chemistry parameters including: creatinine, AST, and blood urea. (See Appendix 3 – Table 4B)

- No clinically significant differences in mean creatinine, sodium, urea, AST or ALT levels at the (U.S.) or (Argentina) were seen between the treatment groups at baseline or post-treatment levels. (See Appendix 3 – Tables 3B and 4B)

Clinically significant individual chemistry laboratories seen post-treatment:

- One patient (#453-0003) had an elevated and clinically significant sodium value post-treatment (153 mmol/L – upper limit of normal was 145 mmol/L). The sponsor reported that this value was repeated a few weeks later and the serum sodium had returned to normal limits.

- Four patients were noted to have elevated and clinically significant AST and/or ALT values post-treatment. These patients (one in the Fertinex® group, two in the approved Gonal-f® group and one in the r-hFSH group) included:
  - One patient (#450-0008) in the new r-hFSH groups had an elevated AST of 97 U/L (normal upper limit is 37 U/L) and elevated ALT of 262 U/L (normal upper limit is 40 U/L). This patient was found to be HIV positive.
  - One patient (#457-0002) in the Fertinex® group had an elevated AST of 76 U/L and an elevated ALT of 122 U/L. The sponsor reported that these liver function tests were repeated two months later, and were within normal limits.
  - Two patients (#432-0003 and #477-0008) in the approved Gonal-f® group had elevated liver function tests post-treatment cycle 3 (Patient #432-0003 had an elevated ALT of 140 U/L and Patient #477-0008) had an elevated AST of 85 U/L). The reason for these mild elevations seen in this group is unknown.

Reviewer's comments:

1. **Gonadotropins are not expected to shift renal or liver function tests. No unexpected shifts or trends in blood chemistry were noted in the treatment groups.**
2. **No clinically significant trends from baseline to post-treatment in chemistry laboratories were across in the three treatment groups. (See Appendix 3 – Tables 3B and 4B). In addition, no significant differences in trends between the group laboratory values pre- and post-treatment were seen between the United States and Argentina.**

a. Vital Signs:

Systolic and diastolic blood pressure was recorded pre- and post-treatment for the three gonadotropin treatment groups. In addition, pulse, temperature and weight pre- and post-treatment in the three treatment groups were evaluated. The most common concern with gonadotropin use is weight gain; weight gain could represent an early sign of ovarian hyperstimulation syndrome (water retention).

- Weight

The sponsor reported mean overall weight gain for all patients at baseline and termination of treatment cycle(s). Mean overall weight gain was defined as mean weight at the pre-study visit compared to mean weight at the end of the last treatment cycle. The sponsor stated that the overall mean change in weight was a 1.8 pound weight gain for all subjects.

The sponsor reported the mean change in weight was:

- 2.2 pound (lb) gain in the new r-hFSH group
- 0.22 lb gain in the approved Gonal-f® group
- 2.6 lb gain in the Fertinex® group

Reviewer's comments:

1. **In this reviewer's opinion, the most accurate changes in weight would occur pre-study and at the end of the first treatment cycle. Seventy percent of patients had a weight after completion of the first treatment cycle. The reviewer's calculated mean change in weight from baseline to endpoint after the first treatment cycle showed:**
   - **2.8 pound (lb) weight loss in the new r-hFSH group**
   - **4.5 lb weight loss in the approved Gonal-f® group**
   - **3.9 lb weight gain in the Fertinex® group**

Reviewer's comments (continued):

The reason for this weight loss in the two groups that used recombinant FSH is unknown. In this reviewer's opinion, because of the incomplete number of patients weighted after completion of the first cycle, it is difficult to predict if a patient will gain or lose weight in a given cycle.

2. **Four subjects who completed treatment cycle one and had significant weight gain noted post-treatment: 3 r-hFSH patients gained more than 7 pounds (9, 13, and 11 pounds) and 1 Gonal-f® patient who gained more than 7 pounds (10.5 pounds).**
3. **No significant change in the three treatment groups (from baseline to post-study) was noted in other vital signs, including: systolic blood pressure, diastolic blood pressure, pulse or temperature was seen in any of the three treatment groups.**

In this reviewer's opinion, it is unknown if the mean weight loss (less than 5 lbs) seen in the two primary efficacy treatment groups (r-hFSH and Gonal-f®) was clinically meaningful. In contrast, the small number of patients (four) with significant weight gain is probably not clinically meaningful.

5. Injection site disorders:

A total of 35 of 275 patients (13% of the treated patient population) experienced injection and/or application site disorders reported as adverse events during the treatment cycle.

The most common injection site reaction seen (pain) occurred was reported as a severe adverse event in:

- 3 patients (3.6%) in the r-hFSH group
- 5 patients (5.3%) in the approved Gonal-f® group
- 3 patients (3.1%) in the Fertinex® group

Reviewer's comment: Injection site disorders appear to be similar across the three treatment groups. (See Appendix 3 – Table 5A). There is no evidence that the new r-hFSH formulation increases local tolerance reactions (as judged to be a severe adverse event).

6. Study termination:

The sponsor stated that reasons for study termination of the treatment cycle: (i.e. withholding gonadotropin therapy [r-hFSH, the approved Gonal-f® formulation or Fertinex®) or human chorionic gonadotropin (hCG) therapy included:

- Clinically significant (moderate or severe) OHSS developing in any treatment cycle.
- WHO grade 3 or 4 adverse event which may have been related to the study drug.
- Protocol violations, including non-compliance and loss to follow-up
- Serious intercurrent illness or significant worsening of intercurrent illness
- Adverse events
- Administrative reasons
- No significant (or imminent) ovarian response after 28 days of treatment
- A significant decline in estradiol levels for two consecutive determinations during ovarian stimulation
- Risk of ovarian hyperstimulation, defined as >3 follicles with a mean diameter ≥ 17 mm or a serum estradiol level >2000 pg/mL
- Patient decision

The major cancellation that results in a safety concern with gonadotropin use is the cancellation of a treatment cycle because of an adverse event.

a. Patients that were cancelled for an adverse event (ovarian hyperstimulation risk in the first treatment cycle included:
    - 2 patients (2.4%) of 83 total patients in the new r-hFSH group
    - 1 patients (1.1%) of 94 total patients in the approved Gonal-f® group
    - 5 patients (5.1%) of 98 total patients in the Fertinex® group

b. Patients that were cancelled for an adverse event (ovarian hyperstimulation risk in the all three treatment cycle included:
    - 7 cycles (4%) of 176 total cycles in the new r-hFSH group
    - 4 cycles (1.9%) of 207 total cycles in the approved Gonal-f® group
    - 10 cycles (4.3%) of 230 total cycles in the Fertinex® group

c. Patients that were cancelled for an adverse event (ovarian hyperstimulation risk in the all three treatment cycle included:
    - 1 patient in the r-hFSH group (#477-0004) was discontinued from continuing a second treatment cycle because of an ectopic pregnancy.

Patients cancelled for ovarian hyperstimulation risk (continued):

- 1 patient in the approved Gonal-f® group (#466-0011) was discontinued from continuing a second treatment cycle because of an ectopic pregnancy

Reviewer's comment: In both the first cycle and all treatment cycles combined the rate of cycle cancellation for the risk of ovarian hyperstimulation appeared to be lower for the r-hFSH group than the other two treatment groups.

7. Multiple birth/miscarriage/ectopic pregnancy rate:

a. The multiple birth rates can be examined using the actual birth data in all treatment cycles of the two primary efficacy treatment groups. (See Appendix 2 – Table 6B).
   - 5 patients had twins (21.7%) and 1 (4.3%) had triplets in the r-hFSH group.
   - 1 patient had twins (5.6%) and none had triplets in the approved Gonal-f® group.

b. The miscarriage rate was reported (See Appendix 2 – Table 6B):
   - 2 miscarriages (5.4%) in the r-hFSH group
   - 7 miscarriages (18.9%) in the approved Gonal-f® group
   - 1 miscarriage (2.3%) in the Fertinex® group

c. The ectopic pregnancy rate was reported (See Appendix 2 – Table 6B):
   - 1 patient (1.2%) in the r-hFSH group
   - 3 patients (3.2%) in the approved Gonal-f® group
   - 1 patient (1.0%) in the group

Reviewer's comments:

1. **The multiple birth rate for the new r-hFSH formulation was not statistically significantly different from the approved Gonal-f® group (See Appendix 2 – Table 6B). In addition, the 22% multiple birth rate seen in the new r-hFSH group in study 22240 is consistent with previous multiple birth rates reported with ovulation induction from 15% - 24%.** [18,19]
2. **The rate of miscarriage is statistically different in the r-hFSH group compared to the approved Gonal-f® group (See Appendix 2 - Table 6B). However, the miscarriage rate in the Gonal-f® group is more consistent with data from a previous ovulation induction trial (study 5727 from NDA 20-378 - miscarriage rate of 22.7%).**

Reviewer's comments (continued):
In this reviewer's opinion, the lower miscarriage rate with r-hFSH compared to the other treatment arm does not represent superiority of r-hFSH, but that the trial is under-powered to demonstrate differences in overall miscarriage rates.

3. **Ectopic pregnancy rates are not clinically different between the two primary efficacy groups treated [i.e. the new r-hFSH formulation and the approved Gonal-f® formulation] (See Appendix 2 – Table 6B).**

In conclusion, although differences were seen in the number of miscarriages between the two groups, there does not appear to be clinically significant changes in multiple birth, miscarriage or ectopic pregnancy rates seen with use of the new r-hFSH formulation. However, it is important to note that study 22240 was not powered to detect clinical differences in these secondary endpoints.

D. Adequacy of Safety Testing

Safety data has been collected for the approved Gonal-f® formulation since the NDA (20-378) was initially submitted in 1993 and subsequent annual reports. Patient exposure has been adequately documented from a safety perspective for the approved Gonal-f® formulation. The safety of the new r-hFSH formulation is based on documentation of clinical non-inferiority to an approved FSH gonadotropin product for each indication.

E. Summary of Critical Safety Findings and Limitations of Data

The current adverse event data for the new Gonal-f® formulation (r-hFSH) for studies 22240 and 21884 are included in the supplement to NDA 20-378 (submitted May 23, 2003). No deaths were reported by the sponsor during the two clinical studies (21884 or 22240). The reported adverse event profile for the new Gonal-f® formulation (r-hFSH) is not substantially different from the safety profile seen in the approved Gonal-f® treatment arm.

In this reviewer's opinion, the safety profile of the new Gonal-f® formulation (r-hFSH) does not appear to be clinically different from a urinary-derived reference gonadotropin product (Fertinex®).

The sponsor reports no new trends or safety issues have been demonstrated in the adverse event profile of the new Gonal-f® formulation (r-hFSH).

VIII. Dosing, Regimen, and Administration Issues

The Chemistry review accepted the lyophilized Gonal-f® product to have [redacted] of the labeled amount in IU and [redacted] of the labeled amount in mcg. For IVF study 21884, applying the same potency limits, the amount can be in the range of [redacted] IU or [redacted] mcg. Even at the highest dose of 450 IU the difference between the [redacted] mcg per dose and [redacted] mcg per dose would be only [redacted] which would be acceptable by current Chemistry standards. Therefore, although the reference r-hFSH was a slightly different amount [redacted] mcg/day in IVF study 21884 compared to [redacted] mcg/day in OI study 22240, for the purposes of the clinical review the difference in amounts (in mcg) used in the two clinical studies can be considered comparable.

The dosage regimens presented in the two clinical studies (21884 and 22240) is similar to the proposed dosage regimens for the proposed indications in the label for the **new r-hFSH formulation**. In the proposed dosage regimen for ovulation induction, the original proposed label for the new **r-hFSH formulation** states that

[redacted]

In the proposed dosage regimen for patients undergoing Assisted Reproductive Technology procedures, the proposed label states those patients:

[redacted]

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Treatment using the approved Gonal-f® was previously approved for treatment of spermatogenesis in male patients May 24, 2000 (NDA 20-378/Supplement 006). The new Gonal-f® formulation was not studied in the sub-fertile male population for clinical equivalence.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Clinical studies of the approved Gonal-f® formulation did not include patients aged 65 and over. Use of the approved Gonal-f® formulation is contraindicated in pregnancy. The two supportive clinical studies (21884 and 22240) did not include geriatric or pregnant patients. However, it is not anticipated that the new r-hFSH formulation would be used in the geriatric or pregnant patient populations.

C. Evaluation of Pediatric Program

The approved Gonal-f® is not indicated for use in pediatric populations and safety and efficacy in such patients have not been established. It is not anticipated that the new r-hFSH formulation would be used in a pediatric population given the current proposed indications.

X. Conclusions and Recommendations

A. Conclusions

This reviewer recommends approval of the new r-hFSH formulation for the proposed indications of ovulation induction in oligo-anovulatory women and multiple follicular development in female patients undergoing assisted reproductive technology (ART).

B. Recommendations

The risk/benefit ratio of using the approved Gonal-f® formulation, and the patient population that benefits from the approved Gonal-f® formulation has been adequately characterized. The new r-hFSH formulation does not appear to differ in either clinical safety or efficacy from approved gonadotropin formulations. In conclusion, the new r-hFSH formulation appears to have a similar risk/benefit ratio to the approved Gonal-f® formulation

Appendix 1

A. Overview of Completed Original Comparative Clinical Trials for NDA 20-378 using the approved Gonal-f® formulation.

1. Study GF5503 – An open-label, randomized IVF-ET trial in Europe that included 123 infertile women after pituitary down-regulation with a gonadotropin-releasing hormone agonist.
   - Primary endpoint was the number of follicles ≥ 14 mm on the day of hCG injection.
   - The mean number of follicles with Gonal-f® was 7.8 and 9.2 for the urofollitropin. This difference was not statistically significant.

2. Study GF5533 – An open label, randomized, IVF-ET trial in the United States that included 120 infertile women after pituitary down-regulation with a gonadotropin-releasing hormone agonist.
   - Primary endpoint was the number of mature, pre-ovulatory (≥ 14 mm) follicles recruited.
   - The mean number of follicles ≥ 14 mm was 7.3 for Gonal-f® and 8.3 with urofollitropin, not statistically different.

3. Study GF5642 - An open label, randomized, ovulation induction trial in Europe and Israel that included 231 patients with anovulatory infertility (WHO Group II) and could receive up to three cycles of therapy.
   - Ovulation was the primary endpoint of the study.
   - The ovulation rate for cycle one was 64% in the Gonal-f® group and 91% in the urofollitropin group. This difference was not considered statistically significant.

4. Study GF5727 – An open label, randomized, ovulation induction trial in the United States that included 232 patients with anovulatory infertility (WHO Group II) and could receive up to three cycles of therapy.
   - Ovulation was the primary endpoint of the study.
   - The ovulation rate for cycle one was 75% for Gonal-f® subjects and 76% for urofollitropin. This difference was not considered statistically significant.

Appendix 1

B. References for the current review:

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* Submitted by the sponsor

Appendix 1

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* Submitted by the sponsor

Appendix 1

C. Principal investigator list for study 21884: (Sponsor Submitted Table IMP21884- 1)

Center Number	City, State/Country	Principal Investigator
001	Flint, MI/USA	Mostafa Abuzeid, MD
002	Cincinnati, OH/USA	Sherif Awadalla, MD
003	Woburn, MA/USA	Steven Bayer, MD
004	Fairfax, VA/USA	Keith Blauer, MD
005	Stony Brook, NY/USA	Kristen Cain, MD
006	Marlton, NJ/SUA	Jerome Check, MD
007	Poland, OH/USA	Robert Collins, MD
008	Bedford, TX/USA	Kevin Doody, MD
009	Norwalk, CT/USA	Michael Doyle, MD
010	Rochester Hills, MI/USA	Michael Hassan Fakih, MD
011	Las Vegas, NV/USA	Jeffrey Fisch, MD
013	Rochester, NY/USA	Kathleen Hoeger, MD
014	Miami, FL/USA	Michael Jacobs, MD
015	San Ramon, CA/USA	Arnold Jacobson, MD
016	Highland Park, IL/USA	Brian Kaplan, MD
017	Hoffman Estates, IL/USA	Vishvanath Karande, MD
018	Chicago, IL/USA	Ralph Kazer, MD
019	New Brunswick, NJ/USA	Ekkehard Kemmann, MD
020	Royal Oak, MI/USA	William Keye, MD
021	Port Jefferson, NY/USA	David Kreiner, MD
022	Margate, FL/USA	Steven Ory, MD
023	Washington, DC/USA	Preston Sacks, MD
024	Ypsilanti, MI/USA	F. Nicholas Shamma, MD
025	Beverly Hills, CA/USA	Mark Surrey, MD
026	Tarzana, CA/USA	Michael Vermesh, MD
027	Pittsburgh, PA/USA	Anthony Wakim, MD
029	Buenos Aires, Argentina	Claudio Chillik, MD
030*	Buenos Aires, Argentina	Nicolas Neuspiller, MD
031*	Buenos Aires, Argentina	Sergio Pasqualini, MD
032*	Buenos Aires, Argentina	Ester Polak, MD
033*	Buenos Aires, Argentina	Carlos Sueldo, MD
034	Buenos Aires, Argentina	Gaston Rey Valzacchi, MD

*Also participated in trial 22240

Appendix 1

D. Principal investigator list for study 22240 (Sponsor submitted table IMP22240-1)

Center Number	City, State/Country	Principal Investigator
054	Cleveland, OH/USA	Tommaso Falcone, MD
068	Livingston, NJ/USA	Margaret G. Garrisi, MD
127	Houston, TX/USA	Randall Dunn, MD
135	Salt Lake City, UT/USA	Matthew Peterson, MD
388	San Ramon, CA/USA	Collin Smikle, MD
397	Miami, FL/USA	Maria Bustillo, MD
404	Kansas City, KS/USA	Valerie Montgomery-Rice, MD
406	Webster, TX/USA	Vicki L. Schnell, MD
410	Boise, ID/USA	Russell A. Foulk, MD
415	Oklahoma City, OK/USA	Gil Haas, MD
432	Torrance, CA/USA	Rifaat Salem, MD
450	Bethesda, MD/USA	Frank Chang, MD
452	San Francisco, CA/USA	Seth Feigenbaum, MD
453	Birmingham, AL/USA	Katheryn L. Honea, MD
454	Huntington, NY/USA	Magdalen E. Hull, MD
455	Charlotte, NC/USA	Brad Hurst, MD
456	Norwalk, CT/USA	Steven Lindheim, MD
457	Baltimore, MD/USA	Howard McClamrock, MD
461	Atlanta, GA/USA	Mark Perloe, MD
463	Las Vegas, NV/USA	Bruce Shapiro, MD
465	West Columbia, SC/USA	Gail F. Whitman-Elia, MD
466	Tampa, FL/USA	Timothy R. Yeko, MD
477	Miami, FL/USA	Fernando Akerman, MD
524	Baton Rouge, LA/USA	Bobby Webster, MD
525	Shawnee Mission, KS/USA	Dan L. Gehlbach, MD
526	Tulsa, OK/USA	Judith Blackwell, MD
356*	Buenos Aires/Argentina	Carlos E. Sueldo, MD
373*	Buenos Aires/Argentina	Rodolfo Sergio Pasqualini, MD
383*	Buenos Aires/Argentina	Nicolás Neuspiller, MD
384*	Buenos Aires/Argentina	Ester Polak de Fried, MD
446	Buenos Aires/Argentina	Liliana Blanco, MD
447	Buenos Aires/Argentina	Jorge A Blaquier, MD
448	Rosario/Argentina	Carlos M. Carizza, MD
451	Buenos Aires/Argentina	Daniel Estofan, MD
462	Buenos Aires/Argentina	Claudio Ruhlmann, MD
502	Buenos Aires/Argentina	Gabriel Fiszbajn, MD

* Also participated in trial 21884

Appendix 2

Table 1A - Demographic characteristic distribution for treated patients in study 21884 (see Sponsor's submitted tables IMP21884-10 and 21884-11)

Characteristic	r-hFSH group	Fertinex® group	p-value*
Age (yrs) N Mean (SD**)	 237 32.5 (3.7)	 239 32.7 (3.5)	p=0.52
Weight (kg) N Mean (SD**)	 236 63.7 (12.2)	 239 63.0 (11.4)	p=0.55
BMI (kg/m^2) N Mean (SD**)	 236 23.8 (3.9)	 239 23.7 (4.1)	p=0.75
Race, n% N White Black Asian Other	 237 195 (82.3) 16 (6.7) 4 (1.7) 22 (9.3)	 239 200 (83.7) 9 (3.8) 6 (2.5) 24 (10.0)	p=0.48

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

*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.

** SD – Standard Deviation

Appendix 2

Table 2A – Baseline characteristic distribution for study 21884 for the treated patient population (see Sponsor's submitted tables IMP21884-12 ,-18, -19 and -20)

Characteristic	r-hFSH group	Fertinex® group	p-value*
Occurrence of the main causes of infertility†			
N	237	239	
Male Factor n(%)	127 (53.6)	125 (52.3)	p=0.78
Tubal Factor n(%)	78 (32.9)	73 (30.5)	p=0.58
Unexplained n(%)	46 (19.4)	43 (18.0)	p=0.69
Endometriosis n(%)	23 (9.7)	34 (14.2)	p=0.13
Other n(%)	26 (11.0)	21 (8.8)	p=0.42
Smoking habits			
N	235	238	
No	208 (88.5)	210 (88.2)	p=0.93
Yes	27 (11.5)	28 (11.8)	
Type of Infertility			
N	237	239	
Primary	130 (54.8)	131 (54.8)	p=0.99
Secondary	107 (45.2)	108 (45.2)	
Duration of Infertility (years)			
N	236	236	p=0.31
Mean (SD**)	4.0 (2.8)	4.3 (3.2)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.
** SD – Standard Deviation
† Subjects may have had more than one infertility diagnosis at the time of presentation to the study.

Appendix 2

Table 3A -Semen analysis parameters for study 21884 for the treated population (see Sponsor's submitted tables IMP21884-25 and -26)

Characteristic	r-hFSH group	Fertinex® group	p-value*
Sperm Morphology n (# reports evaluated) Normal n(%) Abnormal n(%)	 121 46 (38.0) 75 (62.0)	 126 44 (34.9) 82 (65.1)	 p=0.61
Sperm morphology reports missing n(%)	116 (48.5)	113 (47.2%)	
Sperm Concentration (10E6/mL) n Mean (SD**)	 219 53.9 (57.2)	 225 54.7 (50.3)	 p=0.88
Sperm Motility (% A+B) n Mean (SD**)	 219 54.0 (24.8)	 226 54.4 (24.9)	 p=0.88

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.
** SD – Standard Deviation

Table 4A - Screening serum hormonal levels for treated patients in study 21884 (see Sponsor's submitted table IMP21884 -28)

Serum Hormone	r-hFSH group	Fertinex® group	p-value*
FSH (mIU/mL) n Mean (SD**)	 237 7.2 (2.2)	 239 7.1 (1.9)	 p=0.86

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.
** SD – Standard Deviation

Appendix 2

Table 5A – Serum estradiol level (pg/ml) at down-regulation for treated patients in study 21884 (see Sponsor's submitted table IMP21884-29)

Serum Hormone	r-hFSH group	Fertinex® group	p-value*
Age < 35 Estradiol (pg/mL) N Mean (SD**)	 150 24.6 (9.5)	 145 26.2 (11.0)	 p=0.17
Age ≥ 35 Estradiol (pg/mL) N Mean (SD**)	 72 23.4 (9.1)	 73 25.2 (14.4)	 p=0.37
All patients Estradiol (pg/mL) N Mean (SD**)	 222 24.2 (9.4)	 218 25.8 (12.2)	 p=0.11

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.
** SD – Standard Deviation

Appendix 2

Table 6A – Discontinuations for study 21884

Study period	Reason	Not randomized	New r-hFSH	Fertinex	Gonal-F	All
Prestudy	Administrative reasons	2				2
	Discovery of ineligibility	65				65
	Failure of treatment // Discovery of ineligibility	1				1
	Non-compliance	3				3
	Other	18				18
	Patient decision	21				21
Down-regulation	Discovery of ineligibility	1		1		2
	Failure of treatment	3				3
	Other	9		1		10
	Patient decision	1				1
Stimulation	Adverse event		1			1
	Discovery of ineligibility		2			2
	Failure of treatment		7	5	4	16
	Failure of treatment // Adverse event // Other				1	1
	Other		1	1		2
	Patient decision		1			1
	Protocol deviation			1		1
	Risk of OHSS // Adverse event				1	1
Ovum Pick-up	Failure of treatment		4	2	3	9
	Other		10	7	6	23
	Patient decision		1	1	1	3
	Protocol deviation // Non-compliance // Other			1		1
	Risk of OHSS				1	1
After transfer	Patient decision		1			1
All	All	124	28	20	17	189

Appendix 2

Table 7A – Primary efficacy outcome table using the number of fertilized oocytes for the ITT population by type of insemination the patient received (not by treatment randomized) in study 21884.

Outcome	r-hFSH group	Fertinex® group
Median number of fertilized oocytes		
All subjects		
n	237	237
Mean (SD)*	6.3 (4.3)	5.9 (3.9)
Median (min, max)	6 (0, 22)	5 (0, 18)
Median Treatment vs. Fertinex® (95% C.I.)**	1 (0, 1)	
*IVF subjects****		
n	88	92
Mean (SD)*	6.1 (4.4)	5.8 (4.1)
Median (min, max)	6 (0, 20)	5 (0, 18)
Median Treatment vs. Fertinex® (95% C.I.)**	0 (-1, 2)	
*ICSI subjects****		
n	140	134
Mean (SD)*	6.5 (4.3)	5.8 (3.5)
Median (min, max)	6 (0, 22)	5 (0, 17)
Median Treatment vs. Fertinex® (95% C.I.)**	1 (0, 1)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
* SD – Standard Deviation
** Median treatment difference and confidence interval based on the Hodges-Lehmann estimate for treatment difference.
*** For the IVF and ICSI subgroup analyses, 2 IUI subjects and 18 mixed insemination subjects were removed from the analysis.

Appendix 2

Table 8A – Primary efficacy outcome table using fertilized oocytes for the treated population (evaluable patients per protocol) in study 21884 (see Sponsor's submitted table IMP21884 – 31)

Outcome (Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.)	r-hFSH group	Fertinex® group
Median number of fertilized oocytes		
All subjects		
n	216	218
Mean (SD)*	6.7 (4.1)	6.0 (3.7)
Median (min, max)	6 (0, 22)	5 (0, 18)
Median Treatment vs. Fertinex® (95% C.I.)**	1 (0, 1)	
IVF subjects†		
n	83	88
Mean (SD)*	6.4 (4.2)	6.0 (4.0)
Median (min, max)	6 (0, 20)	5 (0, 18)
Median Treatment vs. Fertinex® (95% C.I.)**	0 (-1, 2)	
ICSI subjects†		
n	133	130
Mean (SD)*	6.9 (4.1)	6.0 (3.4)
Median (min, max)	6 (0, 22)	5 (0, 17)
Median Treatment vs. Fertinex® (95% C.I.)**	1 (0, 1)	
< Age 35		
IVF†	52	59
n	7.0 (4.3)	6.1 (3.9)
Mean (SD)*	6 (0, 22)	6 (0, 18)
Median (min, max)	1 (-1, 2)	
Median Treatment vs. Fertinex® (95% C.I.)**		
ICSI†	95	91
n	7.5 (4.4)	5.9 (3.3)
Mean (SD)*	7 (0, 22)	5 (0, 15)
Median (min, max)	1 (0, 2)	
Median Treatment vs. Fertinex® (95% C.I.)**		
≥ Age 35	31	29
IVF†	5.6 (4.0)	5.9 (4.3)
n	5 (0, 17)	4 (0, 17)
Mean (SD)*	0 (-2, 2)	
Median (min, max)		
Median Treatment vs. Fertinex® (95% C.I.)**		
ICSI†	38	39
n	5.3 (2.8)	6.2 (3.7)
Mean (SD)*	5 (1, 12)	6 (0, 17)
Median (min, max)	-1 (-2, 1)	
Median Treatment vs. Fertinex® (95% C.I.)**		

*SD – Standard Deviation ** Median treatment difference and confidence interval based on the Hodges-Lehmann estimate for treatment difference.

†For the IVF and ICSI subgroup analyses, 2 IUI subjects and 18 mixed insemination subjects were removed from the analysis. In addition, this analysis was performed using the insemination method the subject actually received, as opposed to the treatment the patient was randomized to.

Appendix 2

Table 9A – Primary efficacy outcome table using the number of fertilized oocytes documented in study 21884 for the treated population for Argentina (see Sponsor's submitted table IMP21884 – 31)

Outcome	r-hFSH group	Fertinex® group
Median number of fertilized oocytes		
IVF subjects		
n	16	20
Mean (SD)*	4.8 (3.1)	4.6 (2.9)
Median (min, max)	4 (0, 12)	4 (0, 12)
Median Treatment vs. Fertinex® (95% C.I.)**	0 (-2, 2)	
ICSI subjects		
n	36	33
Mean (SD)*	5.0 (2.5)	4.8 (2.6)
Median (min, max)	5 (0, 12)	4 (0, 12)
Median Treatment vs. Fertinex® (95% C.I.)**	0 (-1, 1)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
* SD – Standard Deviation
** Median treatment difference and confidence interval based on the Hodges-Lehmann estimate for treatment difference.

Appendix 2

Table 10A – Primary efficacy outcome table using the number of fertilized oocytes documented in study 21884 for the treated population for U.S. (see Sponsor's submitted table IMP21884 – 31)

Outcome	r-hFSH group	Fertinex® group
Median number of fertilized oocytes		
IVF subjects		
n	67	68
Mean (SD)*	6.8 (4.4)	6.5 (4.2)
Median (min, max)	6 (0, 20)	6 (0, 18)
Median Treatment vs. Fertinex® (95% C.I.)**	0 (-1, 2)	
ICSI subjects		
n	97	97
Mean (SD)*	7.6 (4.4)	6.4 (3.6)
Median (min, max)	7 (1, 22)	6 (0, 17)
Median Treatment vs. Fertinex® (95% C.I.)**	1 (0, 2)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
* SD – Standard Deviation
** Median treatment difference and confidence interval based on the Hodges-Lehmann estimate for treatment difference.

Appendix 2

Table 11A – Primary efficacy outcome table using the number of fertilized oocytes documented in study 21884 for the treated population by country (see Sponsor's submitted table IMP21884 – 31)

Outcome	U.S.	Argentina	p-value
Median number of fertilized oocytes			
All subjects			
n	329	105	
Mean (SD)*	6.8 (4.1)	4.8 (2.7)	p<0.001
Median (min, max)	6 (0, 22)	4 (0, 12)	
IVF subjects			
n	135	36	
Mean (SD)*	6.7 (4.3)	4.7 (2.9)	p=0.01
Median (min, max)	6 (0, 20)	4 (0, 12)	
ICSI subjects			
n	194	69	
Mean (SD)*	7.0 (4.0)	4.9 (2.6)	p=0.001
Median (min, max)	6 (0, 22)	4 (0, 12)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
* SD – Standard Deviation
** p-value based on the unstratified Wilcoxon rank-sum test.

Appendix 2

Table 12A – Secondary efficacy outcome table using the number of total oocytes retrieved in study 21884 for the treated population (see Sponsor's submitted table IMP21884 – 47)

Outcome	r-hFSH group	Fertinex® group	p-value**
Median number of total oocytes retrieved			
All Subjects			
N	218	219	p=0.06
Mean (SD)*	11.9 (6.3)	10.7 (5.9)	
Median (min, max)	11 (1, 39)	9 (0, 38)	
< age 35			
n	148	150	
Mean (SD)*	12.5 (6.3)	10.8 (5.9)	p=0.012
Median (min, max)	12 (2, 39)	9.5 (2, 38)	
≥ age 35			
n	70	69	
Mean (SD)*	10.5 (6.3)	10.4 (5.9)	
Median (min, max)	9 (1, 32)	9 (0, 25)	p=0.81
IVF			
n	85	89	
Mean (SD)*	11.2 (6.4)	10.1 (6.0)	
Median (min, max)	10 (1, 39)	9 (0, 27)	p=0.21
ICSI			
n	133	130	
Mean (SD)*	12.3 (6.2)	11.1 (5.7)	p=0.18
Median (min, max)	11 (4, 32)	10.5 (2, 38)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
* SD – Standard Deviation
** p-value based on the unstratified Wilcoxon rank-sum test

Appendix 2

Table 13A – Secondary efficacy outcome table using the number of metaphase II oocytes documented (for ICSI patients) in study 21884 for the treated population (see Sponsor's submitted table IMP21884 – 49)

Outcome	r-hFSH group	Fertinex® group	p-value**
Median number of metaphase II oocytes retrieved			
All Subjects			
N	218	218	
Mean (SD)*	8.3 (5.4)	7.6 (4.9)	p=0.15
Median (min, max)	8 (0, 24)	7 (0, 25)	
< age 35			
n	148	150	
Mean (SD)*	8.7 (5.6)	7.6 (5.0)	p=0.051
Median (min, max)	8 (0, 24)	7 (0, 25)	
≥ age 35			
n	70	68	
Mean (SD)*	7.5 (5.1)	7.5 (4.7)	p=0.74
Median (min, max)	6.5 (0, 22)	7 (0, 18)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
* SD – Standard Deviation
** p-value based on the unstratified Wilcoxon rank-sum test

Appendix 2

Table 14A – Secondary efficacy outcome table using the number of embryos in study 21884 for the treated population (see Sponsor's submitted table IMP21884 – 53)

Outcome	r-hFSH group	Fertinex® group	p-value**
Median number of embryos			
All Subjects			
N	210	214	
Mean (SD)*	6.5 (4.0)	5.7 (3.5)	p=0.053
Median (min, max)	6 (0, 22)	5 (0, 18)	
< age 35			
n	143	147	
Mean (SD)*	7.0 (4.2)	5.8 (3.3)	p=0.02
Median (min, max)	6 (0, 22)	5 (0, 18)	
≥ age 35			
n	67	67	
Mean (SD)*	5.4 (3.4)	5.6 (3.8)	p=0.89
Median (min, max)	5 (0, 18)	5 (0, 17)	
IVF			
n	79	85	
Mean (SD)*	6.5 (4.3)	6.0 (3.9)	p=0.48
Median (min, max)	6 (0, 19)	5 (0, 18)	
ICSI			
n	131	129	
Mean (SD)*	6.5 (3.9)	5.6 (3.2)	p=0.053
Median (min, max)	6 (0, 22)	5 (0, 17)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
* SD – Standard Deviation
** p-value based on the unstratified Wilcoxon rank-sum test

Appendix 2

Table 15A – Secondary efficacy using clinical pregnancy for study 21884 for the treated population (see Sponsor's submitted table IMP 21884 -80)

Outcome	r-hFSH group	Fertinex® group	p-value*
Clinical pregnancy rate			
N	235	237	p=0.24
Pregnancies (%)	70 (29.8)	83 (35.0)	
< Age 35			
n	158	158	p=0.28
Pregnancies (%)	47 (29.8)	57 (36.1)	
≥ Age 35			
n	77	79	p=0.73
Pregnancies (%)	23 (29.9)	26 (32.9)	
IVF			
n	88	92	p=0.88
Pregnancies (%)	32 (36.4)	35 (38.0)	
ICSI			
n	140	134	p=0.15
Pregnancies (%)	38 (27.1)	48 (35.8)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor. Subjects who received IUI and subjects who were randomized to treatment but did not receive treatment are not included in the analysis. Subjects who received mixed inseminations and became pregnant do not have their pregnancies enter the analysis but are included in the total sample size. In addition, the results for mixed inseminations are not presented.
*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.
** SD – Standard Deviation

Appendix 2

Table 16A – Pregnancy outcome for study 21884 for the treated population (see Addendum 1 of the Integrated Clinical and Statistical Report for study 21884- table-1)

Outcome	r-hFSH group	Fertinex® group	p-value**
N	235	237	
Clinical outcomes n (%)*			
Miscarriage	11 (4.7)	8 (3.4)	p=0.49
Ectopic	3 (1.3)	2 (0.8)	p=0.68
Livebirth	57 (24.3)	74 (31.2)	p=0.10
Unknown	5 (2.1)	1 (0.4)	p=0.12
Singletons***	37 (52.9)	46 (55.4)	p=0.87
Twins	16 (22.9)	23 (27.7)	p=0.58
Triplets	4 (5.7)	5 (6.0)	p=1.0

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor. Subjects who received IUI and subjects who were randomized to treatment but did not receive treatment are not included in the analysis.

* Subjects who received mixed inseminations do not have their clinical outcomes enter the analysis but are included in the total sample size.

*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.

** Percentages are with respect to the total number of pregnancies for IVF and ICSI subjects.

Appendix 2

Table 17A – Secondary efficacy using clinical pregnancy for study 21884 for the treated population for Argentina (see Sponsor's submitted table IMP 21884 -80)

Outcome	r-hFSH group	Fertinex® group	p-value*
Clinical pregnancy rate			
N	56	53	p=0.37
Pregnancies (%)	11 (19.6)	15 (28.3)	
IVF			
n	17	20	p=0.32
Pregnancies (%)	4 (23.5)	8 (40.0)	
ICSI			
n	39	33	p=0.77
Pregnancies (%)	7 (18.0)	7 (21.2)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.
** SD – Standard Deviation

Table 18A – Secondary efficacy using clinical pregnancy for study 21884 for the treated population for U.S. (see Sponsor's submitted table IMP 21884 -80)

Outcome	r-hFSH Group	Fertinex® group	p-value*
Clinical pregnancy rate			
N	172	175	p=0.44
Pregnancies (%)	59 (34.3)	68 (38.9)	
IVF			
n	71	72	p=0.86
Pregnancies (%)	28 (39.4)	27 (37.5)	
ICSI			
n	101	101	p=0.19
Pregnancies (%)	31 (30.7)	41 (40.6)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.
** SD – Standard Deviation

Appendix 2

Table 19A – Secondary efficacy endpoints: duration and total number of FSH ampules used for the treated population in study 21884 (see Sponsor's submitted tables IMP21884-34 and –36)

Outcome	r-hFSH group	Fertinex® group	p-value*
Mean duration of FSH treatment (days)			
N	228	226	p=0.005
Mean (SD**)	9.8 (1.8)	10.2 (1.9)	
< Age 35			
n	152	153	p=0.005
Mean (SD**)	9.7 (1.6)	10.2 (2.0)	
≥ Age 35			
n	76	73	p=0.36
Mean (SD**)	9.9 (2.1)	10.2 (1.8)	
Mean total number of FSH ampules			
N	228	226	p=0.005
Mean (SD**)	26.2 (10.3)	29.1 (11.3)	
< Age 35			
n	152	153	p=0.001
Mean (SD**)	22.7 (8.4)	26.1 (9.4)	
≥ Age 35			
n	76	73	p=0.27
Mean (SD**)	33.2 (10.0)	35.3 (12.4)	

Source: Prepared by Statistical Reviewer from SAS data sets provided by the sponsor.
*The p-value is the contrast between the new r-hFSH formulation and Fertinex®.
** SD – standard deviation

Appendix 2

Table 1B - Demographic characteristic distribution for treated patients in study 22240 (see Sponsor's submitted table IMP22240-13)

Characteristic	New r-hFSH arm	Approved Gonal-f® arm	p-value*
Age (yrs) N Mean (SD**)	 84 29.2 (3.9)	 95 30.7 (3.6)	p=0.009
Weight (kg) N Mean (SD**)	 80 72.4 (14.1)	 90 70.0 (14.4)	p=0.28
BMI (kg/m^2) N Mean (SD**)	 80 26.6 (4.6)	 90 26.2 (4.9)	p=0.60
Race, n% N White Black Asian Other	 84 67 (79.8) 5 (5.9) 3 (3.6) 9 (10.7)	 95 79 (83.2) 6 (6.3) 2 (2.1) 8 (8.4)	p=0.88

*The p-value is the contrast between the new r-hFSH formulation and the approved Gonal-f® formulation.
** SD – Standard Deviation

Appendix 2

Table 2B – Other baseline characteristics for treated patients in study 22240 (see Sponsor submitted tables IMP 22240-14, 22240-15, 22240-16)

Characteristic	r-hFSH group	Approved Gonal-f® group	p-value*
Total patients N	84	95	
Current Smoker n (%) Yes No	 4 (4.8) 80 (95.2)	 11 (11.6) 84 (88.4)	p=0.11
Infertility n (%) Primary Secondary	 50 (59.5) 34 (40.5)	 56 (59.0) 39 (41.0)	p=1.0
Pregnancies n (%) Gravida 0 1 >2 Para 0 1 2 Ectopic 0 1	 50 (59.5) 24 (28.6) 10 (11.9) 68 (80.9) 14 (16.7) 2 (2.4) 83 (98.8) 1 (1.2)	 56 (59.0) 25 (26.3) 14 (14.7) 75 (79.0) 19 (20.0) 1 (1.0) 93 (97.9) 2 (2.1)	 p=0.85 p=0.67 p=1.0
"Acceptable" semen analysis†	***All acceptable***		
Previous therapy for infertility n (%) Yes No	 78 (92.9) 6 (7.1)	 90 (94.7) 5 (5.3)	p=0.76
Duration of Infertility (months) Mean (SD**)	 41.6 (30.8)	 35.1 (22.1)	p=0.11

*The p-value is the contrast between the new r-hFSH formulation and the approved Gonal-f® formulation.

** SD – Standard Deviation

† - The sponsor reported that an "acceptable" semen analysis was determined according to standard practice at each study center.

Appendix 2

Table 3B - Screening serum hormonal levels for treated patients in study 22240 (see Sponsor's submitted table IMP22240-20)

Serum Hormone	r-hFSH group	Approved Gonal-f® group	p-value
Total patients N	85	95	
FSH (mIU/mL) Mean (SD**)	5.8 (2.1)	5.3 (2.2)	p=0.16
Estradiol (pg/mL) Mean (SD**)	50.7 (75.8)	47.9 (45.6)	p=0.76

*The p-value is the contrast between the new r-hFSH formulation and the approved Gonal-f® formulation.
** SD – Standard Deviation

Table 4B – Protocol violations for cycle 1 resulting in cycle cancellation for study 22240 (see Sponsor submitted table IMP 22240-12)

Criteria for exclusion	r-hFSH group	Approved Gonal-f® arm
Number of patients (n)	83	94
1. Non-pregnant patient without progesterone level n(n%)	0	1
2. Concomitant medication intake that could potentially interfere with ovulation	1	3
3. Non-compliance with FSH dosing	2	3
4. Major deviation in entrance criteria	4	1

Appendix 2

Table 5B – Key efficacy outcomes for treated patients in study 22240 in the first cycle

Outcome for Cycle 1	r-hFSH group	Approved Gonal-f® group	p-value
Serum estradiol level on day of hCG (pg/mL) Total n Mean (SD)	 64 509.2 (462.5)	 65 487.85 (475.5)	 p=0.80
Ovulation Rate† Total n n ovulated (%)	 83 59 (71.1)	 94 64 (68.1)	97.5% C.I. (-0.13, 0.18)
Patient administered hCG Total n Yes (% of total)	 84 74 (88.1)	 94 79 (84.0)	 p=0.52
Serum progesterone level (ng/mL) Total n Mean(SD**)	 76 20.8 (21.7)	 78 18.5 (11.7)	 p=0.43
Clinical pregnancy rate (fetal heartbeat) Total n Mean (SD**)	 83 23 (27.7)	 94 18 (19.2)	 p=0.21

†Ovulation as defined by a single mid-luteal serum progesterone level ≥ 10 ng/mL or by a livebirth or by a heartbeat.

*The p-value is the contrast between the new r-hFSH formulation and the approved Gonal-f® formulation.

**SD is standard deviation

Appendix 2

Table 6B – Cumulative pregnancy outcomes for study 22240 for the treated population (see Addendum 1 of the Integrated Clinical and Statistical Report for study IMP22240- table-1)

Clinical Outcome	r-hFSH group n(n%)	Approved Gonal-f® group n(n%)	p-value
	(n=83)	(n=94)	
Total Clinical Pregnancies† n (%)	23 (27.7)	18 (19.1)	p=0.10
Miscarriage	2 (2.4)	9 (9.6)	p=0.06
Ectopic	1 (1.2)	2 (2.1)	p=1.0
Livebirth	22 (26.5)	17 (18.1)	p=0.20
Singletons***	16 (69.6)	16 (88.9)	p=0.25
Twins	5 (21.7)	1 (5.6)	p=0.20
Triplets	1 (4.3)	0 (-)	p=1.0

*The p-value is the contrast between the new r-hFSH formulation and the approved Gonal-f® formulation.
** SD – Standard Deviation
***Percent with respect to total clinical pregnancies for singletons, twins, and triplets
† Clinical pregnancy defined as a fetal sac with a positive heartbeat

Table 7B – FSH exposure for study 22240 for the treated population (see Sponsor's submitted table IMP22240-25)

FSH exposure	r-hFSH group	Approved Gonal-f® group	p-value
	(n=83)	(n=94)	
Number of vials in Cycle 1			
Mean (SD**)	14.4 (9.1)	19.0 (11.0)	p=0.003
Median	11.0	15.0	
Number of days of FSH treatment in Cycle 1			
Mean (SD**)	13.0 (6.2)	16.2 (7.2)	p=0.002
Median	11.0	15.0	

*The p-value is the contrast between the new r-hFSH formulation and the approved Gonal-f® formulation.

Appendix 3

Table 1A: Incidence of the most common adverse clinical events for study 21884 in all cycles (all-subjects-treated group) reported by the sponsor as a percentage of the total patient population (see Sponsor's submitted table IMP21884 – 137).

WHO dictionary included term	New r-hFSH group n(n%)	Approved Gonal-f® group n(n%)	Fertinex® group n(n%)
Total patients	n=237	n=237	n=237
Headache	44(18.6)	33(13.9)	51(21.5)
Abdominal Pain	55(23.2)	56(23.6)	62(26.2)
Ovarian Hyperstimulation	11(4.6)	13(5.5)	13(5.5)
Syndrome	9(3.8)	10(4.2)	8(3.4)
Intermenstrual Bleeding	1(0.4)	0	0
Appendicitis	4(1.7)	1(0.4)	1(0.4)
Breast Pain	4(1.7)	2(0.8)	5(2.1)
Ovarian cyst	19(8.0)	12(5.1)	10(4.2)
Nausea	2(0.8)	1(0.4)	1(0.4)
Flatulence	3(1.3)	2(0.8)	8(3.4)
Dyspepsia	2(0.8)	7(3.0)	3(1.3)
Rhinitis	2(0.8)	1(0.4)	2(0.8)
Sinusitis	1(0.4)	3(1.3)	1(0.4)
Pharyngitis	5(2.1)	3(1.3)	2(0.8)
Dizziness	1(0.4)	0	0
Convulsions			

Appendix 3

Table 2A: A comparison of incidence of selected adverse clinical events for study 21884 in all cycles (all-subjects-treated group) reported by the sponsor as a percentage of the total patient population compared to a previous study (5727) with the approved Gonal-f® product (see Sponsor's submitted table IMP21884-137 and NDA 20-378).

WHO dictionary included term	New r-hFSH group (n%**)	Approved Gonal-f® group (n%**)	Study 5533* - Approved Gonal-f® (n%**)
Total patients	n=237	N=237	n=59
Headache	18.6	13.9	12.5
Abdominal Pain	23.2	23.6	8.9
Ovarian Hyperstimulation Syndrome	4.6	5.5	0
Intermenstrual Bleeding	3.8	4.2	3.6
Nausea	8.0	5.1	5.4
Flatulence	0.8	0.4	3.6

*Study 5533 was an *in vitro* fertilization trial completed for the original NDA (20-378) for the approved Gonal-f® formulation.
** (n%) percentage of patients with the adverse event.

Appendix 3

Table 3A: Study 21884 - Mean Bloodwork Values for Argentina by Treatment Group

	New r-hFSH		Gonal-f®		Fertinex®	
	Prestudy mean (n=55)	***Cycle 1*** mean (n=49)	***Prestudy*** mean (n=56)	***Cycle 1*** mean (n=52)	***Prestudy*** mean (n=54)	***Cycle 1*** mean (n=54)
ALT/SGPT (IU/L)	16.4	14.2	20.6	16.8	14.8 (53)	16.5
AST/SGOT (IU/L)	20.5	17.8	21.6	19.1	19.0 (53)	17.7
Creatinine (mg/L)	9.3	9.4	9.5	9.2	9.4 (53)	9.2
Hematocrit (%)	38.5	38.7	38.1	38.4	39.3	39.6
Hemoglobin (g/dL)	12.6	12.8	12.5	12.6	12.9	13.1
Neutrophils (%)	62.1	60.0	59.5	60.9	61.4	62.8
Urea (g/L)	0.30	0.31	0.27	0.27	0.29 (53)	0.30
WBC (1000/µL)	5.9	6.6	5.6	6.8	6.1	7.3

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

Bloodwork Normal Ranges:

ALT/SGPT	0 to 40 IU/L	AST/SGOT	0 to 35 IU/L	Creatinine	5 to 11 mg/L
Hematocrit	36 to 48 %	Hemoglobin	12 to 16 g/dL	Neutrophils	45 to 70 %
Urea	0.1 to 0.5 g/L	WBC	4 to 9 1000/µL		

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Appendix 3

Table 4A: Study 21884 - Mean Bloodwork Values for United States by Treatment Group

	New r-hFSH		Gonal-f®		Fertinex®	
	Prestudy	***Cycle 1***	***Prestudy***	***Cycle 1***	***Prestudy***	***Cycle 1***
	mean (n)	mean (n)	mean (n)	mean (n)	mean (n)	mean (n)
ALT/SGPT (U/L)	16.5 (180)	18.0 (153)	16.4 (177)	17.9 (154)	16.4 (181)	20.5 (156)
AST/SGOT (U/L)	18.9 (180)	18.3 (153)	19.2 (177)	18.3 (154)	18.9 (181)	19.8 (156)
Creatinine (mg/L)	0.65 (180)	0.61 (153)	0.65 (177)	0.62 (154)	0.64 (181)	0.61 (156)
Hematocrit (%)	38.9 (174)	38.4 (147)	38.9 (179)	38.6 (154)	39.0 (180)	38.6 (152)
Hemoglobin (g/dL)	13.3 (174)	13.2 (147)	13.2 (179)	13.2 (154)	13.3 (180)	13.3 (152)
Neutrophils (%)	57.4 (174)	64.3 (147)	57.2 (179)	65.5 (154)	56.8 (180)	65.0 (152)
Urea (mg/dL)	12.9 (180)	12.3 (153)	12.8 (177)	12.6 (154)	12.5 (181)	12.0 (156)
WBC (1000/μL)	5.7 (174)	7.4 (147)	5.8 (179)	7.4 (154)	5.8 (180)	7.5 (152)

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

Bloodwork normal ranges:

ALT/SGPT	0 to 40 U/L	AST/SGOT	0 to 37 U/L	Creatinine	0.4 to 1.2 mg/L
Hematocrit	37 to 47 %	Hemoglobin	12 to 16 g/dL	Neutrophils	50 to 70 %
Urea	6 to 19 mg/dL	WBC	4 to 11 1000/μL		

Appendix 3

Table 5A: Injection site disorders reported as severe adverse events over the treatment cycle in study 21884

Complaint	r-hFSH group (n)	Approved Gonal-f® group (n)	Fertinex® group (n)
Total patients	83	94	98
Bruising	0	1	0
Local intolerance	1	0	0
Pain	0	0	2

Appendix 3

Table 1B: Incidence of the most common adverse clinical events for study 22240 in all cycles (all-subjects-treated group) reported as a percentage of the total patient population. (see Sponsor's submitted table IMP 22240 – 41)

WHO dictionary included term	New r-hFSH group n(n%*)	Approved Gonal-f group n(n%*)	Fertinex® Group n(n%*)
Total patients	n=83	n=94	n=98
Headache	22(26.5)	27(28.7)	27(27.6)
Abdominal Pain	10(12.0)	6(6.4)	12(12.2)
Ovarian Hyperstimulation Syndrome	6(7.2)	6(6.4)	6(6.1)
Vaginal Hemorrhage	5(6.0)	5(5.3)	4(4.1)
Breast Pain	5(6.0)	3(3.2)	3(3.1)
Ovarian cyst	3(3.6)	4(4.3)	6(6.1)
Nausea	3(3.6)	7(7.4)	8(8.2)
Flatulence	3(3.6)	8(8.5)	4(4.1)
Dyspepsia	2(2.4)	5(5.3)	0
Rhinitis	6(7.2)	6(6.4)	10(10.2)
Sinusitis	5(6.0)	9(9.6)	3(3.1)
Pharyngitis	6(7.2)	5(5.3)	0
Dizziness	2(2.4)	2(2.1)	6(6.1)
Urinary Tract Infection	0	6(6.4)	2(2.0)

* n% - patients (%) experiencing adverse events

Appendix 3

Table 2B: A comparison of incidence of selected adverse clinical events for study 22240 in all cycles (all-subjects-treated group) reported as a percentage of the total patient population compared to a previous study (5727) with the approved Gonal-f® product. (see Sponsor's submitted table IMP 22240 – 41 and NDA 20-378)

WHO dictionary included term	Study 22240 - New r-hFSH n%**	Study 22240 - Approved Gonal-f ® n%**	Study 5727* - Approved Gonal-f® (n%)**
Total patients	n=83	n=94	n=118
Headache	26.5	28.7	22
Abdominal Pain	12.0	6.4	9.3
Ovarian Hyperstimulation Syndrome	7.2	6.4	6.8
Breast Pain	6.0	3.2	4.2
Ovarian cyst	3.6	4.3	15.3
Nausea	3.6	7.4	13.6
Flatulence	3.6	8.5	6.8
Dyspepsia	2.4	5.3	1.7
Rhinitis	7.2	6.4	0.8
Sinusitis	6.0	9.6	5.1
Pharyngitis	7.2	5.3	2.5
Dizziness	2.4	2.1	2.5
Urinary Tract Infection	0	6.4	1.7

* Study 5727 was an ovulation induction trial completed for the original NDA (20-378) for the approved Gonal-f® formulation

** n% - patients (%) experiencing adverse events

Appendix 3

Table 3B: Study 22240 - Mean Bloodwork Values for Argentina by Treatment Group

	New r-hFSH		Gonal-f®		Fertinex®	
	Prestudy mean (n=21)	***Cycle 1*** mean (n=7)	***Prestudy*** mean (n=27)	***Cycle 1*** mean (n=11)	***Prestudy*** mean (n=28)	***Cycle 1*** mean (n=8)
ALT/SGPT (U/L)	15.1	17.6	15.7	13.4	17.9	12.5
AST/SGOT (U/L)	16.4	16.0	17.6	16.7	18.2	15.1
Creatinine (mg/L)	9.2	9.2	9.7	9.2	9.5	9.5
Hematocrit (%)	40.6	38.6	40.5	38.8	40.6	39.7
Hemoglobin (g/dL)	13.2	12.8	13.1	12.6	13.2 (29)	12.9
Neutrophils (%)	64.4	71.9	63.1	69.1	61.0 (29)	67.4
Urea (g/L)	0.31	0.32	0.32	0.33	0.30	0.30
WBC (1000/µL)	6.0	8.6	6.4	7.7	6.4 (29)	8.3

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

Bloodwork Normal Ranges:

ALT/SGPT	0 to 40 U/L	AST/SGOT	0 to 35 U/L	Creatinine	2 to 5 mg/L
Hematocrit	36 to 48 %	Hemoglobin	12 to 16 g/dL	Neutrophils	45 to 70 %
Urea	0.1 to 0.5 g/L	WBC	4 to 9 1000/µL		

Appendix 3

Table 4B: Study 22240 - Mean Bloodwork Values for United States by Treatment Group

	New r-hFSH		Gonal-f ®		Fertinex®	
	Prestudy	***Cycle 1***	***Prestudy***	***Cycle 1***	***Prestudy***	***Cycle 1***
	mean (n)	mean (n)	mean (n)	mean (n)	mean (n)	mean (n)
ALT/SGPT (U/L)	20.7 (62)	18.4 (36)	19.4 (66)	19.9 (28)	20.0 (69)	21.4 (37)
AST/SGOT (U/L)	19.2 (62)	17.9 (36)	19.8 (66)	19.8 (28)	21.0 (69)	20.6 (37)
Creatinine (mg/L)	0.66 (62)	0.66 (36)	0.66 (66)	0.65 (28)	0.67 (69)	0.66 (37)
Hematocrit (%)	40.3 (60)	40.0 (35)	40.6 (63)	40.0 (27)	40.2 (63)	40.2 (36)
Hemoglobin (g/dL)	13.2 (60)	13.1 (35)	13.3 (63)	13.2 (27)	13.2 (63)	13.2 (36)
Neutrophils (%)	59.4 (60)	64.0 (35)	59.0 (63)	63.0 (27)	57.8 (63)	63.1 (36)
Urea (mg/L)	11.8 (62)	11.3 (36)	11.7 (66)	12.2 (28)	11.9 (69)	11.7 (37)
WBC (1000/μL)	6.2 (60)	7.8 (35)	6.3 (63)	7.9 (27)	6.0 (63)	7.6 (36)

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

Bloodwork normal ranges:

ALT/SGPT	0 to 40 U/L	AST/SGOT	0 to 37 U/L	Creatinine	0.4 to 1.2 mg/L
Hematocrit	37 to 47 %	Hemoglobin	12 to 16 g/dL	Neutrophils	50 to 70 %
Urea	9 to 19 mg/L	WBC	4 to 11 1000/μL		

Appendix 3

Table 5B: Injection site disorders reported as severe adverse events (over all three treatment cycles combined) in study 22240 (see Sponsor's submitted table – IMP 22240-Table 42)

Complaint	r-hFSH group (n)	Approved Gonal-f® group (n)	Fertinex® group (n)
Total patients	83	94	98
Bruising	0	1	4
Inflammation	1	1	0
Pain	3	5	3

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MEDICAL OFFICER
I concur. See also M.O. TL Memo.