CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-289

MEDICAL REVIEW(S)

Amended
Bravelle™ Team Leader Review

NDA:	**21-289**
Drug:	**Bravelle™ (purified urofollitropin)**
Indication:	[redacted]
Dosage/Form/Route:	**75 IU lyophilized powder to be reconstituted with 2 ml 0.9% sodium chloride for subcutaneous or intramuscular injection.** **For ovulation induction, the recommended initial dose is 150 IU daily for the first 5 days of treatment. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle™ given should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.** **For** [redacted] **the recommended initial dose is 225 IU. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle™ given should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.**
Applicant:	**Ferring Pharmaceuticals, Inc**
Original Submission Date:	**September 28 2000**
Review Completed:	**June 29, 2001**
Date of Memorandum:	**July 18, 2001**

The purpose of this memorandum is to revise the recommendation on approvability based on new information received about the Database lock date and the timing of this date relative to the submission of the revised statistical plan, which is dated June 6, 2000. An inquiry was made to the Sponsor to provide the study completion date and the database lock date for Study 99-04 (and 99-03). On July 17, 2001, the Sponsor submitted the information that Study 99-04 was completed on June 29, 2000 and the database was locked on August 7, 2000. The date on the

NDA submission is September 28, 2000. The revised statistical plan, which is dated June 6, 2000, was not submitted to the Agency for review until September 14, 2000. It was received by the Agency on September 21, 2000. It is unacceptable to send in a revision to the statistical plan that changes how the data is to be analyzed after the data is accessible for review. Therefore, the clinical review team will not base its review of the approvability for the —— indication on the Sponsor's revised statistical analysis plan, but rather on the original analysis plan in ——— that was powered to show a difference of 1.2 oocytes as a clinically meaningful difference. Referring to the pre-NDA meeting minutes of April 24, 2000, "the Division takes the worst case scenario to be that Follistim® produces a mean of at least 1.2 more oocytes than either delivery method of FSH". Therefore, non-inferiority will be assessed as to whether the Sponsor's calculated confidence intervals can exclude a difference of -1.2 oocytes.

In the ITT analysis for subcutaneously administered Bravelle™, the two-sided 95% confidence interval calculated using Dunnett's procedure (with an analysis for the covariates of age and BMI) for the difference between subcutaneous Bravelle™ and Follistim® is (-2.9, 3.4). In the primary efficacy responder analysis, the two-sided 95% confidence interval calculated using Dunnett's procedure (with an analysis for the covariates of age and BMI) for the difference between subcutaneous Bravelle™ and subcutaneous Follistim® is (-2.4, 3.8). In both of these analyses for subcutaneously administered Bravelle™, the lower bound of the two-sided 95% confidence interval exceeds 1.2 oocyte limit (from the original statistical plan).

In the ITT analysis for intramuscularly administered Bravelle™, the two-sided 95% confidence interval calculated using Dunnett's procedure (with an analysis for the covariates of age and BMI) for the difference between intramuscular Bravelle™ and subcutaneous Follistim® is (-4.1, 2.3). In the primary efficacy responder analysis, the two-sided 95% confidence interval calculated using Dunnett's procedure (with an analysis for the covariates of age and BMI) for the difference between intramuscular Bravelle™ and subcutaneous Follistim® is (-3.6, 2.6). In both of these analyses for intramuscularly administered Bravelle™, the lower bound of the two-sided 95% confidence interval exceeds the 1.2 oocyte limit.

Following the original statistical plan for the analysis of the data, neither subcutaneously administered Bravelle™ nor intramuscularly administered Bravelle™ have been shown to be non-inferior to subcutaneously administered Follistim®. Therefore it is the recommendation of the clinical review team that neither form of Bravelle™ be approved ——— ——

A revised statistical plan was also sent in for Study 99-03 on September 14, 2000. However this revision only clarified that a relative difference of 35% in the percentage of subjects who ovulated is equivalent to an absolute difference of 25%. In the primary efficacy responder population, the Sponsor-calculated one-sided 95% confidence intervals for the differences in percentage were (-1.1%, 22%) for the subcutaneous Bravelle™ group vs. Follistim® and (-5.5%, 19.7%) for the intramuscular Bravelle™ group vs. Follistim®. In women who received hCG (women undergoing ovulation induction with gonadotropins who do not receive hCG do not exhibit normal ovulation), Bravelle™ subcutaneously administered or Bravelle™ intramuscularly administered is non-inferior to Follistim®. Therefore, the recommendation made in the original memorandum that subcutaneously administered and intramuscularly administered Bravelle™ can be approved is unchanged.

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

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/s/

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Bravelle™ Team Leader Review

NDA:	**21-289**
Drug:	**Bravelle™ (purified urofollitropin)**
Indication:	**[redacted]**
Dosage/Form/Route:	**75 IU lyophilized powder to be reconstituted with 2 ml 0.9% sodium chloride for subcutaneous or intramuscular injection.** **For ovulation induction, the recommended initial dose is 150 IU daily for the first 5 days of treatment. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle™ given should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.** **For [redacted] the recommended initial dose is 225 IU. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle™ given should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.**
Applicant:	**Ferring Pharmaceuticals, Inc**
Original Submission Date:	**September 28 2000**
Review Completed:	**June 29, 2001**
Date of Memorandum:	**July 16, 2001**

Background

Follicle stimulating hormone (FSH) is the primary hormone responsible for follicular recruitment and development. The Agency has previously reviewed and approved two products previously classified as urofollitropin (urinary derived preparation of human FSH). The first preparation of urofollitropin that was approved by the Agency was Metrodin, which received approval on September 18, 1986. Fertinex, a highly purified preparation of FSH purified by immunoaffinity

chromatography using murine monoclonal antibody to FSH was subsequently approved on 8/23/96. With this application, Ferring seeks approval for Bravelle™ a highly purified preparation of urofollitropin.

———— containing Protocols FPI FSH 99-03 and FPI FSH 99-04 for Phase 3 clinical trials was opened by Ferring on November 5, 1999. On January 21, 2000, a teleconference between the Agency and Ferring was held to give guidance with respect to statistical issues for the Phase 3 protocols. The Sponsor clarified that the sample size was calculated based on 70% power to detect a relative (not absolute) difference of 35% in ovulation rate. It was further clarified that the Dunnett's procedure should be used for the two FSH comparisons to the active comparator.

A pre-NDA meeting was held on April 24, 2000. The following issues were covered in that meeting:

- The NDA should have 12 months of normal stability data and at least 6 months of accelerated data at the time of submission.
- An accelerated storage condition of 2-8° C is acceptable. Stress testing for further degradation of proteins should be performed (i.e. degradation occurring at room temperature or upon forced oxidation).
- One reference standard for all tests is acceptable.
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- Real time data (12-month real-time data at the time of the submission) is required to set the expiration date.
- Submission of stability data during the review cycle is considered a major amendment and if submitted within 3 months of the goal date, it will extend the review clock of three months.
- Sparse blood sampling for FSH pharmacokinetic (PK) data over the dose range of 75 to 450 IU should be considered.
- A complete bioanalytical assay report including assay validation for FSH should be provided.
- The open label, non-comparative Donor IVF study would not provide evidence for support of a new indication, but rather could be used as supportive data for multiple follicular development in IVF.
- In the review of the NDA, more emphasis will be given to clinical (not chemical) and on-going pregnancies.
- The statistical plan should explicitly describe primary analysis for both trials. If covariates are used, they should be specified.
- The Sponsor should state the statistical hypothesis and propose methodology for testing those hypotheses that are consistent with the way they are formulated.
- The Division understands each trial's (99-03 and 99-04) purpose to be the demonstration of the non-inferiority of either delivery method (IM and SC) of the Sponsor's product (FSH) to Follistim®. These trials should <u>not</u> be trials which simply test for a difference between the treatment groups and then regard a non-statistically significant result as informative. In trial 99-03, the Division takes the 35% relative difference in ovulation incidence (favoring Follistim®) to be the worst case scenario to be ruled out by either a properly constructed hypothesis test or confidence intervals for the ratio of the incidences in the two groups. Similarly, in trial 99-04, the Division takes the worst case scenario to be that Follistim® produces a mean of at least 1.2 more oocytes than either delivery method of FSH.

As a follow-up to concerns regarding Chemistry issues expressed at the April 24, 2000 meeting, an additional meeting between the Agency and Ferring was held on May 1, 2000. Comments from this meeting include:

- The characterization of the protein structure in the IND is inadequate.
- The Agency recommends the following test for characterization:
  Amino acid sequencing;
  Carbohydrate structure determination;
  Disulfide bond structure, if possible;
  Presence of oxidized and/or deaminated forms.
- Information on the specificity of monoclonal antibodies used for Western blots and ELISA should be provided.
- Additional testing to establish the purity profile is also required (i.e., is hCG present in the drug substance?).

NDA 21-289 was submitted on September 28, 2000, received on September 29, 2000 and filed on November 29, 2000.

Chemistry, Manufacturing and Controls (CMC)

The drug substance is purified from large quantities of urine collected by postmenopausal women (the same starting materials as used for the approved menotropins product, Repronex [NDA 21-047]). Fraction C, collected at two steps before the final menotropins drug substance is used for further purification. The drug substance is purified to a specific activity of mg protein. This process is performed by The drug substance is then shipped to SP Pharmaceuticals in Albuquerque, New Mexico for manufacturing of sterile drug product vials. Lactose, phosphate buffer and polysorbate 20 are added to the formulation. After sterile filling into glass vials, the material is lyophilized to powder . The drug product vials are then stoppered and sealed.

The CMC section of the NDA contained extensive deficiencies. These deficiencies are listed in the Appendix to this review. The approvability issues are as follows:

1. The of the drug substance should be characterized with better-defined techniques to demonstrate clear distribution of with a defined range.

2. The specifications for the drug substance are not deemed adequate to assure consistent quality of the drug substance. They should be updated with a specification for Also needed is a valid procedure by which an in-house reference standard can be established from an international standard.

3. The in the manufacture of the drug product should be justified with data.

4. The drug product is to be reconstituted with 0.9% sodium chloride solution; however, no manufacturing information is available for this diluent.

5. The specifications for the drug product should include specifications content by

6. Three copies of complete method validation package should be submitted for validation by Agency's laboratories.

7. The proposed is not acceptable because there is no unified stability protocol, thereby making it very difficult to evaluate the stability of the drug product.

8. Satisfactory inspection results.

From a CMC point of view, the NDA is approvable pending satisfactory resolution of the above issues.

Microbiology

The microbiology review identified the following deficiencies, which were communicated to the Sponsor on January 21, 2001:

The descriptions and data demonstrating the endotoxin removal efficacy of the stopper washing process should be provided. Alternatively, if the stoppers are purchased "endotoxin-free" from the vendor, this should be stated. In this case limits for endotoxin remaining on the stoppers as received should be specified. A schedule for testing incoming stoppers and data demonstrating the amount of residual endotoxin on the stopper, as received, should also be provided. The Sponsor provided a satisfactory response to address these concerns.

Since the goal of any media fill should be the absence of contamination, it is recommended that any positive container be investigated to determine possible causes of contamination. The Sponsor responded that all positive media fill containers are investigated per SOP 05-999 that was provided. No media fill positives were detected from November 1997 to May 1999. This response was satisfactory.

Based on the maximum recommended product dose of 450 IU and the release specification of not more than H, the resulting patient endotoxin dose exceeds the recommended 5 EU/ kg/ hr (based on a 70 kg adult) maximum endotoxin dose. Therefore, the maximum endotoxin specification for this product should be decreased. The Sponsor's responded that the release specification is to be decreased and existing data are being examined to determine the new specification. This response was not considered satisfactory and it was noted that the new final product endotoxin specification should be submitted and reviewed prior to approval. A second information request letter with this final deficiency was sent to the Sponsor on April 21, 2001. The Sponsor responded that the new specification is not more that This results in a maximum dose of 315 EU of endotoxin per hour based on a 70-kg patient and a maximum dose of 450 IU FSH. This response was noted to be satisfactory.

From a microbiology standpoint based on the sterility assurance, the NDA is recommended for approval.

Product Name

On March 13, 2001, the Office of Post-Marketing Drug Risk Assessment (OPDRA) recommended that the tradename Ovanex™ not be accepted. Ferring proposed the new tradename Bravelle™ on April 20, 2001. This tradename was found to be acceptable by OPDRA on May 30, 2001.

Pre-clinical Pharmacology and Toxicology

The pharmacology review focused on the following information: FSH in purified form or as a component of menotropins has a long history of human use. Three non-clinical studies were conducted with Bravelle™. Study 99-2632 was for a single subcutaneous injection to female Sprague-Dawley rats at doses of 4, 40 and 400 IU/kg. The only observed effect was an increase in large tertiary ovarian follicles. Study 99-3407 was an identical study to 99-2632, only conducted in female beagle dogs. The only observed effect was an increase in the number and size of ovarian follicles. Study 99-6528 was a cardiovascular study in 4 female beagles. Subcutaneous administration of urofollitropin of escalating doses of 4, 40 and 100 IU/kg had no effect on BP, HR, MAP and QA, P_R, QT, R_R, or QTc intervals.

On the basis of the cardiovascular dog study showing no effect and the similarity of Bravelle™ to Fertinex® and other approved FSH as well as menotropins products (of which FSH is a component) which have a long history of human use, Pharmacology recommends that from a pre-clinical point of view the NDA is acceptable for approval.

Biopharmaceutics

The pharmacokinetics and bioavailability of Bravelle™ was addressed in 3 studies submitted to the NDA. The following observations and conclusions were made.

The absolute bioavailability of Bravelle™ following subcutaneous and intramuscular administration is unknown. A study was conducted after subcutaneous and intramuscular administration to determine the bioavailability relative to each route of administration. The serum level of FSH after subcutaneous administration is higher than that after intramuscular administration for single and multiple doses. The data obtained after subcutaneous administration appears to be less variable than that obtained after intramuscular administration. Following a single dose of 225 IU, the Cmax is 6.02 mIU/ml and 7.0 mIU/ml after subcutaneous and intramuscular administration, respectively. Following multiple injections of 150 IU for 7 days, the Cmax was 14.8mIU/ml and 11.5 mIU/ml after subcutaneous and intramuscular administration, respectively. The half-life after multiple dose administration appears to be shorter (~20-25 hours) than after single dose administration (~to 40 hours).

A population pharmacokinetic study was conducted in a limited number of subjects (n=16) following subcutaneous or intramuscular injection. The study and the analysis lack adequate power and the number of subjects at each dose level is too small to conclusively conclude dose proportionality. The sponsor claimed that the drug may follow linear (dose proportional) pharmacokinetics because the clearance and volume of distribution did not change with dose. Without the knowledge of the absolute bioavailability of FSH following subcutaneous or intramuscular administration, the data reported for clearance and volume of distribution should be considered as "apparent".

No data is available on drug-drug interactions. No data is available related to metabolism and excretion, the presence and identification of any active metabolites or plasma protein binding. No data is available in subjects with renal or hepatic impairment.

Based on the information that was submitted, the Office of Clinical Pharmacology and Biopharmaceutics finds that the NDA is acceptable.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

The evaluative report of the clinical inspections for NDA 21-289 summarized inspections at four clinical sites. Two of these sites (Dr. Nichols-Greenville, S.C. and [redacted] were found to be in compliance with U.S. Federal Regulations and good clinical investigational practices. Protocol violations were observed at two of the sites (Dr. Dickey-New Orleans, LA and Dr. Thornton-Valencia, CA). However it was determined that none of the violations negatively impact the reliability or integrity of the data submitted in the NDA.

Clinical Efficacy and Safety

Study 99-03 (ovulation induction)

Study 99-03 was a Phase 3, randomized, open-label, multicenter non-inferiority design study conducted in the U.S. to compare the safety and efficacy of Bravelle™ administered by subcutaneous and intramuscular injection to Follistim® administered by subcutaneous injection for ovulation induction in anovulatory or oligoovulatory infertile women. Subjects were to be enrolled if they were infertile and oligoovulatory (cycle length ≥ 35 day but ≤ 40 days with a progesterone not exceeding 4 ng/ml at any time between cycle day 21 and menses during an observational cycle) or anovulatory (historical data of amenorrhea [no more than 2 cycles per year] or cycle length of ≥41 days). Subjects were also required to be nonsmoking, less than 40 years of age, and have normal uterus and ovaries on ultrasound as well as at least one patent fallopian tube with an ipsilateral functioning ovary. A total of 123 subjects were enrolled into the study and started leuprolide acetate for purposes of down regulation of the pituitary. Following down regulation (defined as estradiol ≤45 and endometrial thickness of <6mm), 111 subjects were randomized in a 1:1:1 fashion to 150 IU of Bravelle™ for subcutaneous or intramuscular administration or 150 IU of Follistim® for subcutaneous administration. The starting dose of 150IU for all three treatments were maintained for 5 days and then dosing was individualized within a range of 75 to 450 IU daily for a total duration not to exceed 12 days. Treatment was for 1 cycle only. Ovulation rate (percentage of subjects who achieved a serum progesterone ≥10 ng/ml) was the primary efficacy parameter. Secondary efficacy variables assessed included the number and percentage of subjects who met the criteria to be given hCG (at least one follicle ≥ 14 mm), the number and percentage of subjects who received hCG, mean peak serum estradiol levels, and the number and percentage of chemical, clinical and continuing pregnancies. The results for the intent-to-treat (ITT) analysis are shown in Table 1 adapted from the medical officer's Table 1.

Table 1
Efficacy Outcome by Treatment Group in Ovulation Induction, ITT population.

	Bravelle™ SC N=36	Bravelle™IM N=37	Follistim® N=38
Parameter			
Ovulation-n(%)	25 (69.4)	26 (70.3)	30 (78.9)
Received hCG-n(%)	26 (72.2)	28 (75.7)	35 (92.1)
Mean Peak Serum E_2 pg/ml (SD)	990.9 (676.2)	893.2 (815.2)	1109.0 (788.9)
Chemical Pregnancy-n (%)	11 (30.6)	8 (21.6)	13 (34.2)
Clinical Pregnancy-n (%)	9 (25.0))	7 (18.9)	11 (28.9)
Continuing Pregnancy-n (%)	9 (25.0)	7 (18.9)	10 (26.3)
Subjects with Live Births-n(%)	8 (22.2)	6 (16.2)	4(10.5)

The Sponsor-calculated one-sided 95%confidence intervals for the differences in percentage were (-26.2, 7.2) for the subcutaneous Bravelle™ group vs. Follistim® and (-25.1%, 7.8%) for the intramuscular Bravelle™ group vs. Follistim®. The lower bounds for both subcutaneous Bravelle™and intramuscular Bravelle™ are outside of the absolute 25% difference (35% relative difference) prospectively set by the Sponsor as the tolerable non-inferiority margin. Therefore the ITT analysis did not demonstrate non-inferiority. However, because it is reasonably expected that only those subjects who got hCG could have achieved a normal ovulation, then it is reasonable to look at only those subjects who received hCG in the evaluation of the ovulation rate. When this is done, the ovulation rate is 96.2% for the subcutaneous Bravelle™ group, 92.9% for the intramuscular Bravelle™ group and 85.7% for Follistim. The Sponsor-calculated one-sided 95%confidence intervals for the differences in percentage were (-1.1%, 22%) for the subcutaneous Bravelle™ group vs. Follistim® and (-5.5%, 19.7%) for the intramuscular Bravelle™ group vs. Follistim®. Clearly for women who received hCG, Bravelle™ subcutaneously administered or Bravelle™ intramuscularly administered is non-inferior to Follistim®. It is evident from the above table that there was a discrepancy in the percentage of subjects who received hCG which worked in favor of Follistim® and against Bravelle™. In the study, hCG was to be withheld when the follicular development was inadequate (< 1 follicle of ≥ 14mm) or when according to the investigator there was a risk for ovarian hyperstimulation syndrome (OHSS). The judgement as to the risk of hyperstimulation was to be based on whether there were high serum E_2 levels or excessive development of small to moderate sized ovarian follicles on transvaginal ultrasound evaluation or both. Five subjects treated with subcutaneous Bravelle™, 2 subjects treated with intramuscular Bravelle™ and 2 subjects treated with Follistim® had hCG withheld for risk of OHSS. The Sponsor suggested that in this open-label trial, the investigators were clearly more conservative with giving hCG to subjects treated with the investigative drug, Bravelle™, than they were with subjects treated with the more familiar and approved drug Follistim®. This suggestion is clearly supported by the incidence of OHSS (discussed below) in that a higher percentage of subjects treated with Follistim® developed OHSS (21%) than was the case for those treated with subcutaneous and intramuscular Bravelle™ (8%).

The percentage of chemical, clinical (defined in this NDA as a positive serum hCG and the presence of a fetal heart beat) and continuing pregnancies were numerically greater with the Follistim® treatment group compared to the Bravelle™ treatment groups. No statistical testing for non-inferiority of Bravelle™ to Follistim® on the basis of these secondary efficacy variables was performed.

There were no deaths or dropouts due to adverse events in Study 99-03. There were 4 serious adverse events, all in Bravelle™-treated subjects (2 in the subcutaneous treatment group and 2 in the intramuscular treatment group) and all were OHSS. The incidences of OHSS were 4 of 36 (11%) subjects treated with subcutaneous Bravelle™, 2 of 37 (5.4%) subjects treated with intramuscular Bravelle™ and 8 of 38 (21 1%) subjects treated with Follistim®. Mean injection site pain scores were numerically similar.

Study 99-04 (ART)

Study 99-04 was a Phase 3, randomized, open-label, multicenter study, with a non-inferiority design, conducted in the U.S. to compare the safety and efficacy of Bravelle™ administered by subcutaneous and intramuscular injection to Follistim® administered by subcutaneous injection in subjects who had pituitary desensitization with leuprolide acetate prior to controlled ovarian stimulation as part of an IVF/ET cycle. Subjects were to be enrolled if they were infertile due to tubal factor, endometriosis or unexplained causes. Subjects were to have regular ovulatory menstrual cycles of 24-35 days as well as an objective measure of ovulation and normal FSH, PRL, DHEAS and TSH levels. Subjects were also required to be nonsmoking, less than 40 years of age, and have normal uterus, adnexae and ovaries on ultrasound. A subject whose male partner had an inadequate semen analysis was accepted only if donor sperm were utilized. A total of 193 subjects were enrolled into the study and started leuprolide acetate for purposes of down regulation of the pituitary. Following down regulation (defined as estradiol ≤45 and endometrial thickness of <6mm), 177 subjects were randomized in a 1:1:1 fashion to 225 IU of Bravelle™ for subcutaneous or intramuscular administration or 225 IU of Follistim® for subcutaneous administration. The starting dose of 225 IU for all three treatments were maintained for 5 days and then dosing was individualized to a maximum daily dose of 450 IU for a total duration not to exceed 12 days. Treatment was for 1 cycle only. The primary efficacy variable was the total number of oocytes retrieved per subject. Secondary efficacy variable assessed included the number of mature oocytes retrieved per subject, the number (and percentage) of subjects with oocyte retrieval, the number (and percentage) of subjects with embryo transfer, and the number and percentage of chemical, clinical and continuing pregnancies. The results for the ITT analysis are shown in Table 2 adapted from the medical officer's Table 2.

Table 2
Efficacy Outcome by Treatment Group for IVF, ITT population

	Bravelle™ SC N=60	Bravelle™ IM N=59	Follistim® N=58
Parameter			
Mean oocytes retrieved per subject-n (SD)	13.3 (7.9)	12.2 (7.8)	13.1 (8.7)
Mature oocytes retrieved per subject-n (SD)	9.9 (5.7)	8.7 (5.5)	9.5 (5.6)
Subjects with oocyte retrieval-n (%)	56 (93.3)	55 (93.2)	56 (96.6)
Subjects with embryo transfer-n (%)	54 (90.0)	51 (86.4)	55 (94.8)
Subjects with chemical pregnancies-n (%)	30 (50.0)	23 (39.0)	20 (34.5)
Subjects with clinical pregnancies-n (%)	26 (43.3)	19 (32.2)	18 (31.0)
Subjects with continuing pregnancies-n (%)	25 (41.7)	19 (32.2)	17 (29.3)
Subjects with live births-n (%)	21 (35.0)	15 (25.4	14 (24.1)

The original protocol statistical plan presented power calculations based on the assumption that the expected mean number of oocytes retrieved per cycle is 10 with a standard deviation of 2 in the reference group and that there should be 80% power to detect a change in the number of oocytes of 1.2 (i.e. 10 vs. 8.8) with a sample size of 44 subjects per group. This power calculation stated the properties of the hypothesis test but did not explicitly state the proposed "clinically significant difference" to be ruled out in order to demonstrate non-inferiority. In the April 24, 2000 pre-NDA meeting it was clarified with the Sponsor that for Study 99-04, "the Division takes the worst case scenario to be that Follistim® produces a mean of at least 1.2 more oocytes than either delivery method of FSH". In other words, Bravelle™ would be considered non-inferior to Follistim® if the lower bound of the confidence interval excluded a -1.2 difference (Bravelle™ - Follistim®) in the mean number of oocytes retrieved with Bravelle™ relative to Follistim®. Subsequently, the Sponsor submitted a revised statistical plan which restated the original properties concerning the 1.2 oocyte difference from Follistim®, but also included a revised calculation which states that "there is an 80% power to detect a relative difference of less than 30% if the number of oocytes retrieved in the reference group is 10 with 50 evaluable patients in each group". Although again not explicitly stated, the implied clinical margin is less than 30% of 10 or less than 3 oocytes. A worst case scenario of Bravelle™ producing no more than a **mean 2.99 oocytes less** than Follistim® (based on the revised statistical plan) will be the clinically meaningful difference applied in the non-inferiority analysis.

In the Sponsor's ITT analysis, 10 subjects who did not receive hCG were assigned "zero oocytes". In this analysis, the observed number of follicles retrieved with subcutaneous Follistim®was 13.1 with a standard deviation of 8.7. The observed number of follicles retrieved

in the subcutaneous Bravelle™ treatment arm was 13.3 with a standard deviation of 7.9. The two-sided 95% confidence interval calculated using Dunnett's procedure (with an analysis for the covariates of age and BMI) for the difference between subcutaneous Bravelle™ and Follistim® is (-2.9, 3.4). The Sponsor applied a test of non-inferiority in which the mean number of oocytes retrieved with Bravelle™ treatment was to be no worst than 20% of the mean number of oocytes observed with Follistim®. This proposal for a clinically meaningful difference was not prospectively identified prior to the submission of the NDA. In this analysis of the Sponsor using the post-hoc criterion for a clinically meaningful difference, the lower limit of the two sided 95% confidence interval is within 20% of the observed subcutaneous Follistim® mean (i.e. 2.6 follicles). Not only is this analysis by the Sponsor's unacceptable because of the use of the post-hoc criterion for a clinically meaningful difference, but also (according to the statistical reviewer) it is invalid to use an observed value to apply their 20% standard). **If the clinically meaningful difference of 2.99 oocytes (inferred from the revised statistical plan dated June 6, 2000) is applied, non-inferiority is demonstrated in that the lower limit of the confidence interval does not exceed the 2.99 oocyte limit.**

In the Sponsor's analysis considering only those subjects who received hCG, the primary efficacy responder population, the observed number of follicles retrieved in the subcutaneous Follistim™ group was 13.6 with a standard deviation of 8.5. The observed number of follicles retrieved in the subcutaneous Bravelle™ treatment group was 14.3 with a standard deviation of 7.3. The two-sided 95% confidence interval calculated by the Sponsor using Dunnett's procedure (with an analysis for the covariates of age and BMI) for the difference between subcutaneous Bravelle™ and subcutaneous Follistim® is (-2.4, 3.8). In the analysis of the Sponsor using the post-hoc criterion for a clinically meaningful difference, the lower bound of the difference is less than 20% of the observed mean number of oocytes retrieved with Follistim® (2.7 oocytes). **The lower bound of the Sponsor's calculated confidence interval falls within a 2.99 oocyte difference.**

Subcutaneously administered Bravelle™ meets the modified statistical criteria for non-inferiority to subcutaneously administered Follistim® in both the ITT and the primary responder analyses. The lower bounds of the two-sided 95% confidence interval of the difference between subcutaneously administered Bravelle™ and subcutaneously administered Follistim® for both the ITT and the primary responder populations does not exceed the 2.99 oocyte limit.

The observed number of follicles retrieved in the Sponsor's ITT analysis of the intramuscular Bravelle™ treatment arm was 12.2 with a standard deviation of 7.8. The two-sided 95% confidence interval calculated using Dunnett's procedure (with an analysis for the covariates of age and BMI) for the difference between intramuscular Bravelle™ and subcutaneous Follistim® is (-4.1, 2.3). In the analysis of the Sponsor using the post-hoc criterion for a clinically meaningful difference, the lower limit exceeds 20% of the observed subcutaneous Follistim® mean (i.e. 2.62 follicles). **The lower limit of the 95% two-sided confidence interval exceeds the 2.99 oocyte limit identified in the June 6 revised statistical plan**

In the analysis considering only those subjects who received hCG, the observed number of follicles retrieved in the subcutaneous Follistim™ group was 13.6 with a standard deviation of 8.5. In the primary responder analysis, the observed number of follicles retrieved in the intramuscular Bravelle™ treatment group was 13.1 with a standard deviation of 7.3. The two-sided 95% confidence interval calculated using Dunnett's procedure (with an analysis for the covariates of age and BMI) for the difference between intramuscular Bravelle™ and subcutaneous Follistim® is (-3.6, 2.6). In the analysis of the Sponsor using the post-hoc criterion for a

clinically meaningful difference, the lower bound of the difference is greater than 20% of the observed mean number of oocytes observed with Follistim® (2.7 oocytes). **The lower limit of the 95% two-sided confidence interval exceeds the 2.99 oocyte limit identified in the June 6 revised statistical plan.**

Intramuscularly administered Bravelle™ did not meet the revised statistical plan criterion for non-inferiority to subcutaneously administered Follistim® in either the ITT or the primary responder analysis.

Secondary efficacy variables showed a numerical trend in favor of subcutaneous Follistim® compared to subcutaneous Bravelle™ for number of mature oocytes and subjects with embryo transfer, but a numerical trend in favor of subcutaneous Bravelle™ compared to subcutaneous Follistim® for chemical pregnancies, clinical pregnancies, continuing pregnancies, and patients with live births. Similarly, the secondary efficacy variable showed a numerical trend in favor of subcutaneous Follistim® compared to intramuscular Bravelle™ for number of mature oocytes, subjects with oocyte retrieval and subjects with embryo transfer but a numerical trend in favor of intramuscular Bravelle™ compared to subcutaneous Follistim® for chemical pregnancies, clinical pregnancies, continuing pregnancies, and patients with live births. No statistical testing for non-inferiority of Bravelle™ to Follistim® on the basis of these secondary efficacy variables was performed.

There were no deaths or dropouts due to adverse events in this study. Two serious adverse events occurred. One subject treated with subcutaneous Bravelle™ had an ectopic pregnancy and one subject treated with intramuscular Bravelle™ developed moderate OHSS. Mean injection site pain scores were numerically similar.

Discussion and Conclusions

This reviewer agrees with the primary reviewer that Studies 99-03 and 99-04 establish the safety and efficacy of subcutaneously administered Bravelle™ for ovulation induction and for multiple follicular development (controlled ovarian stimulation) in an ART cycle. I also agree that intramuscularly administered Bravelle™ appears to be safe and efficacious for ovulation induction; however, its efficacy for multiple follicular development in an ART cycle has not been clearly established. I recommend that after the numerous CMC deficiencies are satisfactorily addressed, subcutaneously administered Bravelle™ be approved for the indications of ovulation induction and multiple follicular development in an ART cycle and intramuscularly administered Bravelle™ be approved for the indication of ovulation induction only.

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

Number of Pages Redacted 5

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/s/

Shelley Slaughter
7/27/01 10:56:20 AM
MEDICAL OFFICER

Daniel A. Shames
7/27/01 11:37:41 AM
MEDICAL OFFICER

Medical Officer's Amended Original Clinical Review

NDA Number: 21-289 Name of Drug: Bravelle™

Applicant: Ferring Pharmaceuticals, Inc.

Date of Submissions: September 28, 2000 and March 2, 2001

Date Review Completed: June 29, 2001

Date Review Amended: July 18, 2001

This amended review revises my recommendation for approval of the application from:

> "Approval of this application is recommended from a clinical perspective based on the acceptable demonstration of safety and efficacy in two pivotal clinical trials when the drug is administered subcutaneously (S.C.) to stimulate ovarian follicle development leading to ovulation or retrieval of multiple oocytes in Assisted Reproductive Technology (ART) regimens and pregnancy or when the drug is administered intramuscularly (I.M.) for ovulation induction".
>
> to
>
> "Approval of this application is recommended from a clinical perspective based on the acceptable demonstration of safety and efficacy in one pivotal trial when the drug is administered S.C. or I.M. for ovulation induction in patients who have previously received pituitary suppression".

Recommendation for approval of the indication, "to stimulate ovarian follicle development leading to ovulation or retrieval of multiple oocytes in ART regimens" is rescinded because of new information that came to my attention July 17, 2001 in a response from the applicant to an inquiry from FDA.

[redacted] was submitted to FDA by the applicant November 4, 1999 to conduct study 99-04 in patients undergoing ART. Efficacy was to be based on a statistical analysis plan that was powered to demonstrate a difference of 1.2 oocytes between Bravelle™ and Follistim®, which the applicant determined to be a clinically meaningful difference. This was discussed at the pre-NDA meeting April 24, 2000 with the applicant

and confirmed as being the statistical analysis plan to be relied upon. The study began December 6, 1999 and ended June 29, 2000, two months after the pre-NDA meeting. The database was locked August 7, 2000. A revised statistical plan (dated June 6, 2000) was submitted to the IND September 14, 2000 and the NDA was submitted September 28, 2000 reporting data as analyzed by the revised statistical plan. It is now apparent that the study data should have been evaluated based on the original statistical analysis plan, rather than the revised statistical plan.

Using the original statistical plan proposed by the applicant for the analysis of the data, neither S.C. or I.M. administered Bravelle™ are shown to be non-inferior to S.C. administered Follistim®. Therefore, it is appropriate that Bravelle™ S.C. or I.M. not be approved for [redacted]

Submission dated July 11, 2001 consists of brief clinical summaries for the cases of ovarian hyperstimulation syndrome rated non-serious in studies 99-03, 99-04, and 99-05 in response to a request from FDA. A review of these narratives does not change the safety profile of this drug.

Ridgely C. Bennett, M.D., MP.H.
Medical Officer, HFD-580

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/s/

Ridgely C. Bennett
7/27/01 08:36:49 AM
MEDICAL OFFICER

Shelley Slaughter
7/27/01 10:43:08 AM
MEDICAL OFFICER
I concur. See also Medical Team Leader Memo

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Original Clinical Review

NDA Number: 21-289 Name of Drug: Bravelle™

Applicant: Ferring Pharmaceuticals, Inc.

120 White Plains Road, Suite 400

Tarrytown, New York 10591

Dates of Submissions: September 28, 2000 and March 2, 2001

Dates Submissions Received: September 29, 2000 and March 5, 2001

Date Review Completed: June 29, 2001

EXECUTIVE SUMMARY:

I. Recommendations:

A. Approval of this application is recommended from a clinical perspective based on the acceptable demonstration of safety and efficacy in two pivotal clinical trials when the drug is administered subcutaneously (S.C.) to stimulate ovarian follicle development leading to ovulation or retrieval of multiple oocytes in Assisted Reproductive Technology (ART) regimens and pregnancy or when the drug is administered intramuscularly (I.M.) for ovulation induction. The benefit to risk ratio is favorable.

B. Phase 4 studies are not required. However, the applicant will complete two post marketing studies involving mixed treatment

regimens of Bravelle™ and Repronex® in patients undergoing IVF cycles, for its own purposes.

II. Summary of Clinical Findings:

A. Brief Overview of Clinical Program:

1. Name of Product: Bravelle™ (purified urofollitropin)

2. Therapeutic Class of Product: Infertility

3. Routes of Administration: S.C. and I.M.

4. Clinical Trials: The results of one multicenter, randomized trial comparing Bravelle™ S.C., Bravelle™ I.M., and Follistim® S.C. in 177 subjects undergoing in-vitro fertilization (IVF) and one multicenter, randomized trial comparing Bravelle™ S.C., Bravelle™ I.M., and Follistim® S.C., in 111 anovulatory subjects undergoing induction of ovulation are submitted.

B. Efficacy: Efficacy was demonstrated for

and ovulation induction in patients who have previously received pituitary suppression.

For the IVF study, the primary efficacy variable of oocytes retrieved per person showed no statistically significant differences in either the intent-to-treat (ITT) or primary efficacy responder (received hCG) populations between Bravelle™ S.C., and Follistim® S.C. However, I.M. administered Bravelle™ did not meet the criteria for non-inferiority to S.C. administered Follistim® in either the ITT or the primary responder analysis.

For the ovulation induction study, the primary efficacy variable of ovulation showed no statistically significant differences in either the intent-to-treat or primary efficacy responder populations between Bravelle™ S.C., Bravelle™ I.M., and Follistim® S.C.

according to the sponsor. However, when tests for non-inferiority were applied, Bravelle™ S.C. and I.M. did not meet the test for non-inferiority in the ITT analysis, but did so in the primary efficacy responders analysis.

The efficacy for both indications when Bravelle is administered S.C. is the same as that reported for other drugs marketed for the same indications.

C. Safety: Safety testing is adequate. Each subject was treated for one cycle for a maximum of 12 days. Monitoring and follow-up were adequate. The most serious adverse effect was the development of the ovarian hyperstimulation syndrome (OHSS). During ART treatment, OHSS occurred in 9 Bravelle™ treated subjects including 3 serious cases requiring hospitalization. During ovulation induction, OHSS occurred in 6 Bravelle™ treated subjects including 2 serious cases. Most cases were associated with early pregnancy. OHSS occurred in 6.8% of treated subjects. OHSS is recognized as the most serious adverse event occurring with the use of gonadotropins in infertility treatment and is adequately addressed in the proposed labeling for this product.

No drug/drug interaction studies have been conducted for Bravelle™ in humans. However, it is well known that hCG can make the occurrence of OHSS worse and the labeling clearly states that usually, in cases where OHSS may be developing prior to hCG administration, hCG should be withheld. If severe OHSS occurs, treatment must be stopped and the patient should be hospitalized. A physician experienced in the management of OHSS or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

Subjects with an active or prior history of substance abuse, including alcohol and tobacco, were excluded from the clinical trials, except for subjects who stopped tobacco usage at least 3 months prior to baseline visit. It is expected that when the drug is marketed, smokers may also be treated with it. This should not result in any significant increased risk to those smokers.

The warnings in the labeling are adequate. The safety of this drug is the same as that for other drugs used for the same indications.

There are no unresolved safety issues.

D. Dosing: The dosage and administration are the same as that utilized in similar drug products that have had a good safety record over years of marketing. The effects of dosing are closely monitored by the use of vaginal ultrasound and serum estradiol levels. There are no dose modifications recommended and there are no unresolved dosing/administration issues.

E. Special Populations: This drug is being approved for conditions that occur only in women. The drug is not indicated for use in pediatric patients and safety and efficacy in such patients have not been established. Clinical studies did not include subjects over the age of 39 years. This drug is contraindicated in pregnancy. The safety and efficacy of the drug in renal and hepatic insufficiency have not been studied. The vast majority of subjects in the trials (70% -83%) were Caucasian with about 5%-17% African-Americans. Racial and ethnic differences are not likely to be of any significant concern regarding efficacy or safety of the drug product.

CLINICAL REVIEW:

I. Introduction and Background:

A. Established Drug Name: Purified urofollitropin

B. Proposed Trade Name: Bravelle™

C. Therapeutic Class: Infertility

D. Indications: Bravelle™ in conjunction with hCG, is indicated for

s and ovulation induction in patients who have previously received pituitary suppression.

E. Dosage:

Infertile patients with oligo-anovulation: The dose of Bravelle™ to stimulate development of ovarian follicles must be individualized for each patient. The lowest dose consistent with achieving good results based on clinical experience and reported clinical data should be used.

The recommended initial dose of Bravelle™ for patients who have received GnRH agonist or antagonist pituitary suppression is 150 IU daily for the first 5 days of treatment. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle™ should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.

If patient response to Bravelle™ is appropriate, hCG (5000 to 10,000 USP units) should be given 1 day following the last dose of Bravelle ™. The hCG should be withheld and the patient should be advised to refrain from intercourse if the serum estradiol is greater than 2000 pg/mL, if the ovaries are abnormally enlarged or if abdominal pain occurs. These precautions may reduce the risk of OHSS and multiple gestations. Patients should be followed closely for at least 2 weeks after hCG administration. If there is inadequate follicle development or ovulation without subsequent pregnancy, the course of treatment with Bravelle™ may be repeated. The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation becomes apparent from the indices employed for the determination of progestational activity. In the light of the foregoing indices and parameters mentioned, it should become obvious that, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use Bravelle™ .

Assisted Reproductive Technologies: The recommended initial dose of Bravelle™ is 225 IU for patients undergoing IVF who have received GnRH agonist or antagonist pituitary suppression. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle™ given should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.

Once adequate follicular development is evident, hCG (5000-10,000 USP units) should be administered on the day following Bravelle™ to induce final follicular maturation.

F. Age Groups Studied: 18-39 years of age.

G. Brief Overview of Clinical Studies: The NDA includes two controlled studies (FPI FSH 99-03 and FPI FSH 99-04) in oligo-anovulatory patients for ovulation induction and in patients undergoing IVF which constitute the pivotal efficacy trials. Both studies had randomized, open label, parallel group, multi-center designs comparing Bravelle™ S.C., Bravelle™ I.M., and Follistim® S.C. FPI FSH 99-05 is a single treatment arm multi-center study evaluating the use of Bravelle™ S.C. in an IVF cycle using egg donation. This small, uncontrolled, incomplete study provides some additional safety data.

H. Armamentarium for Indications: There are many drugs already marketed for these indications.

I. Prior FDA Reviews and Issues: At the pre NDA meeting April 24, 2000, the applicant was informed that the Division does not view study 99-05 as adequate to support labeling for use of Bravelle™ in donor IVF programs. The applicant agreed with this assessment.

J. Foreign Marketing Status: Bravelle™ has not been marketed in any country.

II. Clinically Relevant Findings from Pharmacology Studies: Bravelle™ is a highly purified preparation of urofollitropin extracted from the urine of post-menopausal women. It contains 75 IU of FSH biological activity and 1-2% of LH biological activity in each vial based on the WHO validated rat bioassay used as a release test for all gonadotropin drug products, according to the applicant.

Because gonadotropins including urofollitropins and recombinant follitropins have been approved and extensively used as fertility treatments for oligoanovulatory patients and patients undergoing *in vitro* fertilization, the clinical program for Bravelle™ did not include pharmacology studies in humans.

III. Human Pharmacokinetics and Bioavailability: Single and multiple dose (7 daily doses) studies of Bravelle™ administered S.C. and I.M.were conducted in normal healthy female subjects. Sixteen subjects were evaluated for S.C. administration followed by twelve subjects for I.M. administration. The sample size for the I.M. group was reduced from 16 to 12 after analysis of the S.C. results demonstrated sufficient intersubject consistency to allow an accurate determination of classical PK parameters with the smaller number of subjects. The formulation used in these studies was a sterile, lyophilized powder containing 75 IU of FSH activity, plus [redacted] of lactose as the monohydrate, 0.005 mg tween, sodium phosphate buffer (sodium tribasic and phosphorus acid), and 1-2 % of leuteinizing hormone activity. This formulation is identical to the planned commercial formulation. Over all, S.C. administration appeared to provide slightly higher AUC and Cmax than I.M. administration.

IV. Description of Clinical Data and Sources:

A. Overall Data: The data are from the clinical trial program conducted exclusively at academic and private practice centers specializing in fertility treatment. All principal investigators were reproductive endocrinologists.

B. Disposition of Subjects: Treatment was for one cycle and the maximum duration of treatment was 12 days.

In the induction of ovulation study, 123 subjects were enrolled and started on leuprolide acetate for down regulation. Twelve subjects were not

randomized because of the failure to down regulate. A total of 111 subjects were randomized and all were evaluable for safety and efficacy assessments in the intent-to-treat analyses.

In the IVF study, 193 subjects were enrolled and started on leuprolide acetate for down regulation. Sixteen of these subjects were not randomized because they did not achieve down regulation, they were pregnant, or they had an abnormal Pap smear. A total of 177 subjects were randomized and all were evaluable for safety and efficacy in the intent-to-treat analyses.

C. Postmarketing Experience: None

D. Literature Search: None

V. Clinical Review Methods:

A. Description of How Review was Conducted: The two pivotal studies were reviewed in their entirety. The small, uncontrolled, donor egg study is incomplete and the interim report for this study was reviewed in detail.

The outcome of pregnancies for both pivotal studies were re-computed because the applicant was using the total number of subjects as the denominator rather than the number of pregnant subjects. The applicant had also combined pregnancies from the donor egg study inappropriately with the pregnancies from the IVF study which required re-computation of their analyses. Subjects in the donor egg study were healthy, younger women with lower body mass index than those in the IVF clinical study. Adverse events were also re-computed because one column in the table had an incorrect denominator and some numbers in the other column were incorrect. The numbers in the WARNINGS section concerning OHSS also were re-computed because they were incorrect.

B. IND Evaluation: ——— was reviewed in detail. The clinical protocols were originally submitted to the IND, where they were evaluated and found to be acceptable.

C. Data Quality and Integrity: The Division of Scientific Investigations audited four clinical investigators. Two of the investigators conducted their studies satisfactorily. In an audit of medical records and case report forms of 24 subjects of a third investigator, it was found that one subject did not meet inclusion criteria and source documents for a second subject could not be located. Audit of the fourth clinical investigator revealed some unsatisfactory findings, but none of the unsatisfactory findings were of sufficient magnitude to call into question the integrity of the data.

D. Ethical Issues: The informed consent documents were satisfactory.

E. Financial Disclosure: The sponsor provided appropriate documentation for financial disclosure information for all investigators. There was no disclosure of financial interests that could bias the outcome of the clinical trials.

VI. Review of Efficacy:

A. Findings in Light of Proposed Labeling Claims: Study 99-04 supports the claim of multiple follicular development (controlled ovarian stimulation) when Bravelle™ is administered S.C. in patients who have previously received pituitary suppression and study 99-03 supports the claim of ovulation induction in patients who have previously received pituitary suppression when Bravelle™ is administered S.C. or I.M.

B. Integrated Summary of Efficacy: Efficacy results for one randomized, active controlled, multi-center study in IVF and one randomized, active controlled, multi-center study of ovulation induction are summarized in tables 1 and 2. The patients underwent pituitary suppression with a GnRH agonist before staring Bravelle™ administration. The first study evaluated 177 patients undergoing IVF, of whom 119 received 225 IU Bravelle™ daily for 5 days. This was followed by individual titration of the dose

from 75 to 450 IU daily based on ultrasound and estradiol levels. The total duration of dosing did not exceed 12 days.

The second study evaluated 111 anovulatory patients undergoing ovulation induction, of whom 73 received 150 IU Bravelle™ daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol levels. The total duration of dosing did not exceed 12 days. Ovulation was defined as a mid-luteal progesterone of $\geq$ 10 ng/mL on a blood sample drawn on day 6, 7, 8, or 9 following the administration of hCG.

Table 1

(Sponsor's Tables 3 and 5, Vol. 8H)

Efficacy Outcome by Treatment Group for IVF (Intent to Treat)

	Bravelle™ SC	Bravelle™ IM	Follistim® SC
Parameter	N=60	N=59	N=58
Total oocytes Retrieved per Patient (SD)	—	—	—
Mature oocytes Retrieved per Patient (SD)	—	—	—
Pts w/oocyte Retrieval (%)	56 (93.3)	55 (93.2)	56 (96.6)
Pts w/Embryo Transfer (%)	54 (90.0)	51 (86.4)	55 (94.8)
Pts w/Chemical Pregnancy (%)	30 (50.0)	23 (39.0)	20 (34.5)
Pts w/Clinical Pregnancy (%)	26 (43.3)	19 (32.2)	18 (31.0)
Pts w/Continuing Pregnancy (%)	25 (41.7)	19 (32.2)	17 (29.3)
Pts w/Live Births (%)	21 (35.0)	15 (25.4)	14 (24.1)

For the IVF study, the primary efficacy variable, oocytes retrieved per patient, showed no clinically significant or statistically significant differences in either the intent-to-treat or primary efficacy responder (received hCG) populations between Bravelle™ S.C., and Follistim® S.C.

However, I.M. administered Bravelle™ did not meet the criteria submitted in the revised statistical plan for non-inferiority to S.C. administered Follistim® in either the ITT or the pimary responder analysis.

Secondary efficacy variables showed a numerical trend in favor of Follistim® compared to Bravelle™ S.C. for patients with oocyte retrieval, patients with embryo transfer, and peak estradiol levels, but a numerical trend in favor of Bravelle™ S.C. compared to Follistim® for chemical pregnancies, clinical pregnancies, continuing pregnancies, and patients with live births.

Table 2

(Sponsor's Tables 3 and 5, Vol. 8A)

Efficacy Outcome by Treatment Groups in Ovulation Induction (Intent to Treat)

	Bravelle™ SC	Bravelle™ IM	Follistim® SC
Parameter	N=36	N=37	N=38
Ovulation (%)	25 (69.4)	26 (70.3)	30 (78.9)
Received hCG (%)	26 (72.2)	28 (75.7)	35 (92.1)
Mean Peak Serum E_2 (pg/mL) (SD)	990.9 (676.2)	893.2 (815.2)	1109.0 (788.9)
Chemical Pregnancy (%)	11 (30.6)	8 (21.6)	13 (34.2)
Clinical Pregnancy (%)	9 (25.0)	7 (18.9)	11 (28.9)
Continuing Pregnancy (%)	9 (25.0)	7 (18.9)	10 (26.3)
Pts. w/Live Births (%)	8 (22.2)	6 (16.2)	4 (10.5)

For the ovulation induction study, the primary efficacy variable of ovulation showed no statistically significant difference in the primary efficacy responder (received hCG) populations between Bravelle™ S.C., Bravelle™ I.M., and Follistim S.C. Although a higher percentage of Follistim® patients received hCG, among the primary efficacy responders, higher percentages of Bravelle™ S.C. (96.2%) and Bravelle™ I.M. (92.9%) patients ovulated compared to Follistim® S.C. (85.7%).

The ITT analysis failed to demonstrate non-inferiority of Bravelle™ S.C. and I.M. compared to Follistim® S.C.

Secondary efficacy variables showed no significant differences for rates of chemical, clinical and continuing pregnancies among the three treatments despite the fact there was a significant difference in both the number of subjects who met the criteria for hCG and the number of subjects who received hCG among the three treatment groups. The difference favored Follistim® S.C. This was true for both the ITT and primary efficacy responder analyses. The study was open label and there is evidence that some investigators were more conservative in their judgments on administering hCG to patients receiving the investigational drug compared to Follistim®. Clinical pregnancies were defined as a positive serum hCG and the presence of an intrauterine gestational sac on ultrasound examination.

C. Statistician's Evaluation: Please refer to statistician's review.

VII. Integrated Review of Safety:

A. Findings as Reflected in Proposed Labeling: Safety is based on the data from studies 99-03 and 99-04 with the additional data from a small (30 patients), uncontrolled donor egg study (study 99-05). Each subject was treated for one cycle for a maximum of 12 days. Monitoring and follow-up were adequate. The most serious adverse effect was the development of OHSS. During ART treatment, OHSS occurred in 9 Bravelle™ treated subjects including 3 serious cases requiring hospitalization. During ovulation induction, OHSS occurred in 6 Bravelle™ treated subjects including 2 serious cases. Most cases were associated with early pregnancy. OHSS occurred in 6.8% of Bravelle™ treated subjects and

4.2% of Follistim® treated subjects. Adverse events by body systems are accurately detailed in the draft labeling.

B. Patient Exposure and Safety Assessment: Patients were treated for one cycle and for a maximum of 12 days. All adverse events, whether or not felt to be related to Bravelle™, were tabulated and are detailed in the draft labeling. The drug is safe, based on the reported adverse events. Patient exposure was adequate and the safety profile for Bravelle™ has been adequately defined.

C. Specific Findings of Safety Review: There were no deaths or adverse dropouts in the studies.

Pain on injection was assessed by each patient on each day of follitropin treatment using a digital scale numbered 1 through 10, with 1 being no symptoms and 10 being severe pain.

In the ovulation induction study, there were no statistically significant differences in mean injection site pain score on any day of treatment or for the cumulative mean, Days 1 to 12. Pain scores were generally in the mild range and no patient interrupted or discontinued treatment because of local intolerance to the injection whether given S.C. or I.M.

In the IVF study, the applicant concluded that Bravelle™ administered S.C. or I.M. demonstrated clinically meaningfully better local tolerance with less injection site pain and irritation than Follistim® S.C. The difference was related to the difference in Polysorbate 20 concentrations, according to the applicant. However, if this were true, one would expect to have found the same difference in the ovulation induction study. Such a difference was not found even though both studies were conducted during the same time frame and with the same differences of Polysorbate-20 in the Bravelle™ and Follistim®. Therefore, one cannot determine that there is, in fact, a real difference in local tolerability favoring Bravelle™ over Follistim®.

VIII. Assessment of Dosing/Regimen/Administration Issues: The dosage and administration are the same as that utilized in similar drug products that have had a good safety record

over years of marketing. The effects of dosing are closely monitored by the use of vaginal ultrasound and serum estradiol levels. There are no dose modifications recommended and there are no unresolved dosing/administration issues.

IX. Use in Special Populations:

A. This drug is being approved for conditions that occur only in women.

B. This drug is not indicated for use in pediatric patients and safety and efficacy in such patients have not been established.

C. The vast majority of subjects in the trials (70% -83%) were Caucasian with about 5%-17% African-Americans. Racial and ethnic differences are not likely to be of any significant concern regarding efficacy or safety of the drug product.

D. Clinical studies did not include subjects over the age of 39 years. This drug is contraindicated in pregnancy. The safety and efficacy of the drug in renal and hepatic insufficiency have not been studied.

X. Conclusions and Recommendations:

A. Overall Risk-Benefit Analysis: The clinical studies described in this NDA document the therapeutic efficacy and safety of Bravelle™ administered S.C. to stimulate ovarian follicle development leading to ovulation or retrieval of multiple oocytes in ART regimens and pregnancy. Bravelle™ administered I.M. was shown to be at least as effective, safe and well-tolerated as Follistim®, a commercially available, widely used recombinant follitropin to stimulate ovarian follicle development leading to ovulation in anovulatory patients, but not for retrieval of multiple oocytes in ART regimens.

Given the long history of efficacy and safety in clinical practice of follitropins and the good results for Bravelle™ obtained in the clinical studies reported in this NDA, the benefit to risk relationship of Bravelle™ S.C. is favorable for ovulation induction and ART regimens. The benefit to risk relationship of Bravelle™ I.M. is favorable only for ovulation induction.

The benefits of the drug outweigh its risks.

B. Remaining Unresolved Issues: None.

C. Summary of Major Issues Regarding Draft Package Insert:

1. The applicant included efficacy results from a small, incomplete, non-randomized, open-label, single treatment arm, study of Bravelle™ SC to stimulate multiple follicle development in donor egg patients. The patient population in this study was different from the IVF clinical study. These patients were healthy, younger women with lower body mass index than those in the IVF clinical study. At the pre NDA meeting April 24, 2000, the applicant was informed that the Division does not view this study as adequate to support labeling for use of Bravelle™ in donor egg programs. The applicant agreed with our assessment. The applicant was asked to remove the table giving the efficacy outcomes from donor egg patients.

2. The applicant was asked to revise a warning statement that said that Bravelle™ is a potent gonadotropic substance capable of causing mild to severe adverse reactions in women to "----capable of causing OHSS with or without pulmonary or vascular complications in women".

3. The applicant was asked to add a warning statement that OHSS occurred in 3 of 30 (10.0%) Bravelle™ treated women during the small ART clinical study of donor egg patients.

4. The applicant was asked to revise the tables of multiple pregnancies using the number of pregnant subjects as the denominator rather than the total number of subjects (pregnant and non-pregnant subjects) so that the high percentage of multiple gestations that occur with purified urofollitropin (and all other gonadotropins) is emphasized.

5. The applicant was asked not to combine pregnancy rates for the IVF and donor egg studies, but to report the outcome of pregnancies from the IVF study only, excluding the outcomes from the donor egg study.

6. The applicant was asked to include OHSS as a possible adverse reaction to be discussed with the patient prior to therapy with Bravelle™.

7. The applicant was asked to include a statement regarding mutagenic test results in the "Carcinogenesis and Mutagenesis" section of the labeling.

8. The applicant was asked to mention the number of Bravelle™ treated patients in the "Adverse Reactions" section upon which the safety of Bravelle™ was based.

9. The applicant was asked to correct the title of the table of patients with adverse events to indicate that these were events that occurred in 0.8% or more of patients.

10. The applicant was asked to correct the table of adverse events to reflect the correct number and percentage of OHSS occurrences.

11. The applicant was asked to revise the table of adverse events to include adverse events occurring in the donor egg study as well as the pivotal clinical studies.

12. The applicant was asked to add directions for using Bravelle™ to the labeling.

13. The applicant was asked to delete the column in the tables that referred to the active comparator.

14. The applicant was asked to revise the indication to indicate that Bravelle™ was indicated for [redacted]

D. Approval of this application is recommended for S.C. administration of Bravelle™ for ovulation induction [redacted] of Bravelle™ for ovulation induction (and not for ART regimens).

E. Post-Marketing Risk Management Studies Recommended: None.

XI. Individual Study Reviews:

A. Protocol 99-03:

1. Title of the Study: A Randomized, Open-Label, Parallel Group, Multi-Center Efficacy Study in Anovulatory or Oligoovulatory Infertile Female Patients Comparing Purified FSH S.C., Purified FSH I.M. and Follistim® S.C. for Ovulation Induction.

2. Investigators and Study Sites:

Leo Bonaventura	Indianapolis, IN
Steven Corson	Plymouth Meeting, PA
Andre Denis	Woodstock, GA
Seth Feigenbaum	San Francisco, CA
Peter Horvath	Albany, NY
Paul Kaplan	Eugene, OR
Robert Kaufman	Mt. Pleasant, SC
Eric Knochenhauer	Birmingham, AL
Vivian Lewis	Rochester, NY
John Mattox	Phoenix, AZ
Milton McNichol	Houston, TX
Paul Miller	Greenville, SC
Kelly Padigas	Providence, RI
Grant Schmidt	Dublin, OH
Stephen Somkuti	Abington, PA

3. Objectives of the Study: To determine the therapeutic efficacy of purified FSH S.C. and I.M. compared to Follisitim® S.C. for ovulation in anovulatory or oligoovulatory infertile female patients.

   To determine the safety and tolerance of purified FSH S.C. and I.M. compared to Follistim® S.C.

4. Rationale for the Study: Various urofollitropin and recombinant FSH products have been approved for treatment of anovulatory and oligoovulatory female infertility. This study was conducted to evaluate and compare the therapeutic efficacy and safety of purified FSH S.C. and I.M. and Follistim ® S.C. in anovulatory or oligoovulatory infertile female patients for ovulation induction.

5. Method of Assignment to Treatment: Subjects were randomly assigned to receive one of the three treatments using a randomization code.

6. Number of Subjects: A total of 123 subjects were enrolled (started leuprolide). A total of 111 subjects were randomized and analyzed.

7. Duration of Treatment: One cycle, maximum treatment of 12 days.

8. Inclusion Criteria: Subjects were eligible for enrollment in the study if they met all of the following criteria:

   (a) Signed Informed Consent Form, prior to screening evaluations.

   (b) Nonsmoking females between the ages of 18-39 years (treatments must start before the 40^{th} birthday) and premenopausal.

   (c) Infertile due to ovulatory dysfunction as described in (d) below.

   (d) Be anovulatory or oligoovulatory. If the cycle length was ≥ 41 days or the patient was amenorrheic (no more than two menstrual periods per year), anovulation was presumed and historical data confirming anovulation was to be provided. If the cycle length was ≤ 40 days, anovulation documentation had to be updated before starting the treatment. In order to do this, the patient was to undergo one cycle of observation during which serum P_4 levels were to be measured at seven day intervals beginning on cycle day 21 and continuing for a maximum of three P_4 levels or until menses began. Anovulation was confirmed if P_4 levels did not exceed 4 ng/mL at any time.

   (e) A body mass index (BMI) not greater than 38.

   (f) Had spontaneous menses or positive response to progesterone withdrawal in past three months.

(g) Plasma follicle stimulating hormone and prolactin must have been within normal range. In the event of a thyroid stimulating hormone (TSH) level abnormality, the TSH level must have been deemed as not clinically significant by the Investigator or due to exogenous thyroid medication.

(h) Plasma levels of the following hormones were required to be below these limits at screening:

DHEA-S: Did not exceed > 50% the upper limit of the normal range as determined by investigator.

Total Testosterone: Did not exceed > 50% the upper limit of the normal range as determined by investigator.

(i) Clinically normal baseline hematology, clinical chemistry and urinalysis parameters at screening. Negative serum hepatitis B surface antigen unless vaccinated, hepatitis C antibody and human immunodeficiency virus (HIV) antibody and rapid plasma reagin tests.

(j) Normal transvaginal ultrasound with respect to uterus and ovaries.

(k) Patency and apparent normalcy of at least one fallopian tube with ipsilateral functional ovary as documented by recent (within three years) hysterosalpingography or laparoscopy. If the patient had undergone any pelvic surgery, and/or pelvic inflammatory disease (PID) since this assessment, a repeat hysterosalpingography or laparoscopy was required prior to the patient's entry.

(l) Normal uterine cavity by hysteroscopy, hysterosalpingography or sonohysterography, in the past 3 years.

(m) Male partner with recent (within 6 months) semen analysis which showed normalcy according to the revised WHO criteria.

(n) No treatment with fertility modifiers for at least one month prior to screening for this study.

(o) Negative serum pregnancy test (qualitative) prior to beginning therapy (pre-leuprolide acetate).

(p) Had willingness to participate in the study and comply with the protocol.

(q) Had desire to become pregnant.

9. Exclusion Criteria: The study enrolled patients who did not have any of the following exclusion criteria:

(a) Any medical or surgical condition which in the opinion of the Investigator or Sponsor interfered with the absorption, distribution, metabolism or excretion of the drug.

(b) Any clinically significant systemic disease (e.g., insulin dependent diabetes).

(c) Any concomitant medications that would interfere with evaluation of study medications. Specifically, any non-study hormonal therapy (except for thyroid medication), prostaglandin inhibitors (NSAIDs, including aspirin) and psychotropic agents (phenothiazines, major tranquilizers) at the time of study entry.

(d) Any pregnancy within three months prior to screening.

(e) Previous treatment with more than one cycle of gonadotropin.

(f) Ovarian cysts with a mean diameter $\geq$ 15 mm that had persisted for more than one cycle or ovarian endometrioma on ultrasound.

(g) Presence of clinically significant uterine fibroids.

(h) Abnormal bleeding of undetermined origin of the reproductive tract.

(i) Active substance abuse by history (including alcohol) or tobacco use within 3 months of the baseline study visit.

(j) History of chemotherapy (except for gestational conditions) or radiotherapy.

(k) Known stage III or IV endometriosis or evidence of such disease by laparoscopy or ultrasound.

(l) Was currently breast feeding, pregnant or had a contraindication to pregnancy.

(m) Refused or was unable to comply with the requirements of the Protocol for any reason, including scheduled clinic visits and laboratory tests.

(n) Had documented intolerance or allergy to any FSH.

(o) Had participated in any experimental drug study within proceeding sixty (60) days.

10. Trial Period: January 12, 2000 to July 19, 2000

11. Dosage and Mode of Administration: The starting doses of purified FSH S.C. and I.M. and Follistim® were 150 IU daily for 5 days, followed by individualized dosing within a range of 75 to 450 IU daily for a total duration not exceeding 12 days.

12. Primary and Secondary Efficacy Assessments: Ovulation rate was the primary efficacy parameter. Ovulation was defined as a progesterone of $\geq$ 10 ng/mL on day 6, 7, 8, or 9 after the administration of hCG. Secondary efficacy variables included the number and percentage of subjects who met hCG criteria (at least one follicle $\geq$ 14 mm), the number and

percentage of subjects who received hCG, mean peak serum estradiol, and the number and percentage of chemical, clinical, and continuing pregnancies. Clinical pregnancies were defined as a positive serum hCG and the presence of an intrauterine gestational sac on ultrasound examination.

Table 3

(Sponsor's Tables 3 and 5, Vol. 8A)

Efficacy Outcome by Treatment Groups in Ovulation Induction (Intent to Treat)

	Bravelle™ SC	Bravelle™ IM	Follistim® SC
Parameter	N=36	N=37	N=38
Ovulation (%)	25 (69.4)	26 (70.3)	30 (78.9)
Received hCG (%)	26 (72.2)	28 (75.7)	35 (92.1)
Mean Peak Serum E_2 (pg/mL) (SD)	990.9 (676.2)	893.2 (815.2)	1109.0 (788.9)
Chemical Pregnancy (%)	11 (30.6)	8 (21.6)	13 (34.2)
Clinical Pregnancy (%)	9 (25.0)	7 (18.9)	11 (28.9)
Continuing Pregnancy (%)	9 (25.0)	7 (18.9)	10 (26.3)
Pts. w/Live Births (%)	8 (22.2)	6 (16.2)	4 (10.5)

The tolerable non-inferiority margin relative to Follistim® was an absolute 25% difference in the percentage of ovulating women. The applicant's confidence intervals for the differences in percentages between the two test groups, FSH S.C., FSH I.M. and the Follistim® control group were (-26.2%, 7.2%) and (-25.1%, 7.8%) respectively for the ITT analysis. This suggests that FSH S.C. and I.M. may be inferior to Follistim® based soley on the ITT analysis. However, it is reasonable to analyze only those patients who received hCG in the evaluation of ovulation rates since only those patients are expected to ovulate. When this is done, the ovulation

rate is 96.2% for the Bravelle™ S.C. group, 92.9% for the Bravelle™ I.M. group, and 85.7% for the Follistim® group. The applicant-calculated one-sided 95% confidence intervals for the differences in percentage were (-1.1%, 22%) for the Bravelle™ S.C. group versus Follistim® and (-5.5%, 19.7%) for the Bravelle™ I.M. group versus Follistim®. Clearly, for patients who received hCG (primary efficacy responders), Bravelle™ S.C. and I.M. are non-inferior to Follistim®.

The hCG was withheld from 10 subjects treated with FSH S.C., 9 subjects treated with FSH I.M. and 3 subjects treated with Follistim®.

There were two main reasons for patients not receiving hCG. One was inadequate response in terms of the protocol specified criterion of at least one follicle $\geq$ 14 mm. Four of the ten FSH S.C. patients, 6 of the 9 FSH I.M. patients and one of the 3 Follistim® patients (total= 11 patients) did not get hCG because of this. The second reason was risk of OHSS as perceived by the investigator. This clinical judgment was sometimes based on high E_2 levels, sometimes on numerous small to moderate sized ovarian follicles on transvaginal ultrasound and sometimes on both. None of these patients had any clinical evidence of OHSS and some clinical decisions not to give hCG were ultraconservative and based on the desire to avoid any risk of possible multiple pregnancies. Five of the 10 FSH S.C. patients, 2 of the 9 FSH I.M. and 2 of the 3 Follistim® patients (total=9) did not get hCG because of this. Additionally, one FSH S.C. patient chose to discontinue after 8 doses even though she met criteria for receiving hCG because of personal, not medical, reasons and one FSH I.M. patient was discontinued because of investigator error even though she met hCG criteria.

There were approximately equal numbers of patients not getting hCG for reasons representing opposite poles of pharmacological response, i.e., inadequate response versus risk of OHSS.

Because Ferring FSH is an investigational drug, investigators may have made more conservative judgments concerning hCG administration than for Follistim®. The incidence of OHSS in this study was 4 of 36 for FSH S.C. (2 serious), 2 of 37 for FSH I.M. (none serious) and 4 of 38 for Follistim® (2 serious). This suggests the investigators were more familiar with Follistim® and made more aggressive clinical judgments for patients receiving it.

Mean peak serum estradiol levels were not significantly different.

Chemical, clinical, and ongoing pregnancies were numerically similar between the treatment groups. No test of statistical significance was applied.

13. Safety Assessment: There were no deaths or dropouts due to adverse events.

Four serious adverse events occurred, two subjects each in the FSH S.C. and Follistim® S.C. groups. All four events were OHSS.

There were no significant differences among the treatment groups for subjects with any adverse events.

There were no statistically significant differences in mean injection site pain scores on any day of treatment.

14. Disposition of Subjects: One hundred twenty-three (123) patients were enrolled in the study and started on leuprolide acetate for down regulation. Twelve (12) of the patients were not randomized to follitropin because of failure to down regulate to the protocol specified criteria of $E_2 \leq 45$ pg/mL and endometrial lining < 6mm on transvaginal ultrasound. One hundred (111) patients were randomized to follitropin therapy and all were evaluable for efficacy and safety assessments in the intent-to-treat analyses.

15. Protocol Violations: Numerous minor protocol deviations occurred during the conduct of this study. Most did not affect the evaluability of the patients and were related to small exceptions prospectively made by Ferring for such things as semen analysis, E_2 levels and the timing of screening procedures.

16. Demographic Characteristics: Overall, the subjects in all three treatment groups were comparable demographically and medically. Mean

testosterone was significantly higher in the FSH I.M. group at screening, but this was not clinically meaningful (FSH I.M. – 67.6 ng% versus FSH S.C. – 49.8 ng%, p= 0.031).

17. Reviewer's Comments: **This study was conducted generally along the lines that other urofollitropins have followed. It was a one cycle study in down regulated subjects who met all of the inclusion criteria and had none of the exclusion criteria. Sample size and statistical methodologies were agreed upon before the study began by the applicant and FDA. I agree with the applicant's assessment and conclusions regarding this study.**

Purified FSH S.C. and I.M. were equal in effectiveness to Follistim® S.C. for ovulation induction in oligo-anovulatory down regulated patients in this study. Pregnancy rates were also equivalent. There were a few significant differences favoring Follistim® over FSH S.C. or I.M. for the secondary efficacy variables of meeting hCG criteria and receiving hCG, but these pharmacological differences were small and did not translate into differences in clinical outcomes. The mean dose and duration of treatment with FSH I.M. was slightly more than for FSH S.C. and Follistim® S.C., probably because of the pharmacokinetic (bioavailability) differences related to the two routes of administration.

All three treatments demonstrated excellent and equivalent safety and local tolerance.

Purified FSH administered S.C. or I.M. is a safe and effective urofollitropin for ovulation induction.

B. Protocol 99-04:

1. Title of the Study: A Randomized, Open-Label, Parallel-Group, Multicenter, Efficacy Study Comparing Purified FSH S.C., Purified FSH I.M. and Follistim® S.C. in Female Patients Undergoing *In-Vitro* Fertilization.

2. Investigators and Study Sites:

Sandra Bello	Houston, TX
Jack Crain	Charlotte, NC
Richard Dickey	New Orleans, LA
David Frankfurter	Providence, RI
Benjamin Gocial	Plymouth Meeting, PA
Marsha Gorrill	Portland, OR
Hilton Kort	Atlanta, GA
William Kutteh	Memphis, TN
John Nichols	Greenville, SC
Michael Steinkampf	Birmingham, AL
Melvin Thornton	Valencia, CA

3. Objectives of the Study: To determine the therapeutic efficacy of purified FSH S.C. and I.M. compared to Follistim® S.C. in terms of follicles recruited, percentage cycles with oocyte retrieval and percentage cycles with pregnancy.

   To determine the safety and tolerance of purified FSH S.C. and I.M. compared to Follistim® S.C.

4. Rationale for the Study: Various urofollitropin and recombinant FSH products have been approved for development of multiple follicles in females participating in an ART program. This study was conducted to evaluate and compare the therapeutic efficacy and safety in patients undergoing I.V.F. of purified FSH S.C., purified FSH I.M. and Follistim®, an approved product, for this indication.

5. Method of Assignment to Treatment: Subjects were randomly assigned to receive one of the three treatments using a randomization code.

6. Number of Subjects: A total of 193 subjects were enrolled and started on leuprolide acetate for down regulation. Sixteen of these subjects were not randomized to follitropin because they failed to down regulate to estradiol ≤ 45 pg/mL and endometrial lining < 6mm on transvaginal ultrasound, they were pregnant, or they had an abnormal Pap smear. A total of 177 subjects were randomized to follitropin therapy and all were evaluable for efficacy and safety in the intent-to-treat analysis.

7. Duration of Treatment: One cycle, maximum treatment of 12 days.

8. Inclusion Criteria: Subjects were eligible for enrollment in the study if they met all of the following criteria:

   (a) Signed Informed Consent Form, prior to screening evaluations.

   (b) Nonsmoking females between the ages of 18 and 39 years (treatment initiation must have taken place before reaching 40th birthday) and premenopausal.

   (c) Regular, ovulatory menstrual cycles of 24-35 days and documented evidence of at least one of the following:

   - mid-luteal phase serum Progesterone level > 5ng/mL, or
   - late luteal phase endometrial biopsy with < 3 days lag, or
   - biphasic basal body temperature chart, or
   - history of mid-cycle urinary LH surge within one of the past two (2) cycles.

   (d) Early follicular phase (day 2-3, preferably day 3) serum E_2, FSH, PRL, T, DHEA-S and TSH levels within the normal limits for the clinical laboratory, or considered not clinically significant by investigator. These tests had to be performed within sixty (60) days of entry into the study (start of leuprolide acetate treatment).

   (e) Clinically normal baseline hematology, clinical chemistry (SMA-24), and urinalysis parameter values, negative serum hepatitis B surface antigen, negative hepatitis C antibody, negative human immunodeficiency virus (HIV) antibody and negative rapid plasma reagin tests within 60 days prior to leuprolide acetate treatment.

   (f) Seropositive for rubella and varicella prior to leuprolide acetate.

   (g) Infertility attributable to or in association with either tubal factors, endometriosis (stage I or II only), or unexplained causes. Couples with an associated male factor could be enrolled only if donor sperm was to be used.

   (h) Male partner with recent (within previous six months) semen analysis. If screening semen analysis was borderline, the couple

could be accepted into the study if a second sample obtained was adequate. Donor sperm could be used, if indicated.

(i) Presence of both ovaries, without evidence of abnormality, as detected by vaginal ultrasound performed prior to study enrollment.

(j) Normal transvaginal ultrasound with respect to uterus and adnexae (no hydrosalpinges, no uterine fibroids).

(k) A minimum of one cycle without treatment with fertility modifiers immediately prior to screening.

(l) A minimum of one cycle without IVF/ART treatment immediately prior to screening.

(m) Hysterosalpinography, hysteroscopy, or sonohysterogram documenting a uterine cavity consistent with expected normal function within the previous three (3) years prior to the baseline visit.

(n) Negative serum pregnancy test (qualitative) prior to beginning therapy (pre-leuprolide acetate).

(o) Desire to become pregnant.

9. Exclusion Criteria: The study enrolled patients who did not exhibit any of the exclusion criteria listed below:

(a) Presence of any clinically relevant systemic disease (e.g., insulin-dependent diabetes mellitus).

(b) Surgical or medical condition which in the judgment of the Investigator or Sponsor would interfere with absorption, distribution, metabolism, or excretion of the drugs used.

(c) Any pregnancy within last three months prior to screening.

(d) A body mass index of greater than 34.

(e) More than three previous ART cycles.

(f) Previous IVF or ART failure related to either a sperm/fertilization problem which resulted in unsuccessful fertilization or an ART with a poor response to gonadotropins. Poor response was defined as development of ≤ 2 mature follicles or history of two previous cycle cancellations prior to oocyte retrieval due to poor response.

(g) Presence of abnormal uterine bleeding of undetermined origin.

(h) Active or prior history of substance abuse, including alcohol and tobacco (Patients who had discontinued tobacco use at least three months prior to the baseline visit would be allowed).

(i) History of chemotherapy (except for gestational conditions) or radiotherapy.

(j) Breast feeding, or pregnant at screening or had any contraindication to pregnancy.

(k) Refused or was unable to comply with the requirements of the Protocol for any reason, including scheduled clinic visits and laboratory tests.

(l) For male partner, obvious leukospermia (> 2 million WBC/mL) or signs of infection in semen sample within past two months; if either of these conditions existed, male could be treated with antibiotics and retested prior to his spouse receiving leuprolide acetate.

(m) Documented intolerance or allergy to any gonadotropin or follitropin product.

(n) Participated in any experimental drug study within the sixty days prior to screening for this study.

10. Trial Period: December 6, 1999 to June 29, 2000.

11. Dosage and Mode of Administration: The assigned follitropin was administered S.C. or I.M. as a single daily dose of 225 IU for 5 days after which doses were individualized to a maximum daily dose of 450 IU for a total duration not exceeding 12 days.

12. Primary and Secondary Efficacy Assessments:

Table 4

(Sponsor's Tables 3 and 5, Vol. 8H)

Efficacy Outcome by Treatment Group for IVF (Intent to Treat)

	Bravelle™ SC	Bravelle™ IM	Follistim® SC
Parameter	N=60	N=59	N=58
Total oocytes Retrieved per Patient (SD)			
Mature oocytes Retrieved per Patient (SD)			
Pts w/oocyte Retrieval (%)	56 (93.3)	55 (93.2)	56 (96.6)
Pts w/Embryo Transfer (%)	54 (90.0)	51 (86.4)	55 (94.8)
Pts w/Chemical Pregnancy (%)	30 (50.0)	23 (39.0)	20 (34.5)
Pts w/Clinical Pregnancy (%)	26 (43.3)	19 (32.2)	18 (31.0)
Pts w/Continuing Pregnancy (%)	25 (41.7)	19 (32.2)	17 (29.3)
Pts w/Live Births (%)	21 (35.0)	15 (25.4)	14 (24.1)

For the IVF study, the primary efficacy variable, oocytes retrieved per patient, showed no statistically significant differences in either the intent-to-treat or primary efficacy responder (received hCG) populations between Bravelle™ S.C., and Follistim® S.C. However, I.M. administered Bravelle™ did not meet the criteria for non-inferiority to S.C. administered Follistim® in either the ITT or the primary responder analysis. A clinically meaningful difference of no more than 2.99 oocytes was applied in the non-inferiority analysis. The 95% confidence intervals for the mean differences FSH S.C. - Follistim® and FSH I.M.-Follistim® in the ITT analysis were (-2.9 oocytes, 3.4 oocytes) and (-4.1 oocytes, 2.3 oocytes) respectively. The 95% confidence intervals for the mean differences FSH S.C. - Follistim® and FSH I.M. - Follistim® in the

primary responder analysis were (-2.4) oocytes, 3.8 oocytes) and (-3.6 oocytes, 2.6 oocytes), respectively.

Secondary efficacy variables showed a numerical trend in favor of Follistim® compared to Bravelle™ S.C. for patients with oocyte retrieval, patients with embryo transfer, and peak estradiol levels, but a numerical trend in favor of Bravelle™ S.C. compared to Follistim® for chemical pregnancies, clinical pregnancies, continuing pregnancies, and patients with live births.

13. Safety Assessment: There were no deaths or adverse dropouts in this study. Two serious adverse events occurred. One subject receiving Bravelle™ S.C. had an ectopic pregnancy and one subject receiving Bravelle™ I.M. had OHSS, which was moderate in nature.

Pain on injection was assessed by each patient on each day of follitropin treatment using a digital scale numbered 1 through 10, with 1 being no symptoms and 10 being severe pain.

In the IVF study, the applicant concluded that Bravelle™ administered S.C. or I.M. demonstrated clinically meaningfully better local tolerance with less injection site pain and irritation than Follistim® S.C. The difference was related to the difference in Polysorbate 20 concentrations, according to the applicant. However, if this were true, one would expect to have found the same difference in the ovulation induction study. Such a difference was not found even though both studies were conducted during the same time frame and with the same differences of Polysorbate 20 in the Bravelle™ and Follistim®. Therefore, one cannot determine that there is, in fact, a real difference in local tolerability favoring Bravelle™ over Follistim®.

14. Disposition of Patients: A total of 193 subjects were enrolled and started on leuprolide acetate for down regulation. Sixteen of these subjects were not randomized to follitropin because they failed to down regulate to estradiol $\leq$ 45 pg/mL and endometrial lining < 6mm on trangsvaginal ultrasound, they were pregnant, or had an abnormal Pap smear. A total of 177 subjects were randomized to follitropin therapy and all were evaluable for efficacy and safety in the intent-to-treat analysis.

15. Protocol Violations: Numerous minor protocol deviations occurred during the conduct of this study. Most did not affect the evaluability of the patients and were related to small exceptions prospectively made by

Fetring for such things as semen analysis, E_2 levels and the timing of screening procedures.

16. Demographic Characteristics: Overall, the subjects in all three treatment groups were comparable demographically and medically.

17. **Reviewer's Comments: This study was conducted generally along the lines that other urofollitropins have followed. It was a one cycle study in down regulated subjects who met all of the inclusion criteria and had none of the exclusion criteria. Sample size and statistical methodologies were agreed upon before the study began by the applicant and FDA.**

FSH S.C. was at least equal in effectiveness to Follistim® S.C. in terms of primary and secondary efficacy variables assessed in this study. In addition there were strong and consistent numerical trends favoring FSH S.C. over Follistim® for several secondary efficacy variables including chemical, clinical and continuing pregnancies in both the intent-to-treat and primary efficacy responder analyses. FSH administered I.M. required slightly higher doses because of pharmacokinetic and bioavailability differences, but still did not meet the pre-specified criteria for non-inferiority to S.C. administered Follistim® in either the ITT or the primary responder analysis.

Pregnancy rates in the FSH S.C. and I.M. treatment groups for one cycle of therapy were excellent compared to historical, published data for various follitropins.

All three treatments showed excellent safety profiles with no dropouts due to adverse events.

The applicant concluded that Bravelle™ administered S.C. or I.M. demonstrated clinically meaningfully better local tolerance with less injection site pain and irritation than Follistim® S.C. The difference was related to the difference in Polysorbate 20 concentrations, according to the applicant. However, if this were true, one would expect to have found the same difference in the ovulation induction study. Such a difference was not found even though both studies were conducted during the same time frame and with the same differences of Polysorbate 20 in the Bravelle™ and Follistim®. Therefore, one cannot determine that there is, in fact, a real difference in local tolerability favoring Bravelle™ over Follistim®.

Bravelle™ administered S.C. is a safe and effective drug for use in patients undergoing in vitro fertilization. However, its efficacy for multiple follicular development in an ART regimen when administered I.M. has not clearly been established.

C. Protocol 99-05: This is an incomplete, ongoing, uncontrolled clinical trial of egg donor patients that is supportive of the ART indication and adds some safety data. An interim report was submitted September 28, 2000 and a second interim report submitted March 2, 2001. Thus far, 30 of 40 planned donor patients have completed study.

At the pre NDA meeting April 24, 2000, the applicant was informed that the Division does not view study 99-05 as adequate to support labeling for use of Bravelle™ in donor IVF programs. The applicant agreed with this assessment and is not requesting a separate indication for this patient population.

The patient population in this study is different from the IVF clinical study (protocol 99-04). The patients in this study were healthy, younger women, with lower body mass index than those in the IVF pivotal clinical trial. Bravelle™ was given at a dose of 225 IU for the first 4 days (not for the first 5 days as in protocol 99-04) and then individualized.

This is a non-comparative single treatment arm study evaluating purified FSH S.C. for egg donor patients as part of an IVF program. A separate study, FPI FSH 99-04, was designed to be the pivotal efficacy study of purified FSH for IVF and generated comparative data against an approved recombinant follitropin, Follistim®. Donor IVF is not considered by the reproductive endocrinology community or by regulatory authorities to be a separate and distinct therapeutic indication from IVF. Therefore, this study was designed to be informational and provide additional safety and efficacy data in this variation of IVF. The mean number of oocytes retrieved for the 30 completed donor patients is 14.4 (SD-7.07). This is similar to the 13.3 (SD-7.9) oocytes retrieved per patient in the pivotal IVF study. No unexpected adverse events occurred in this egg donor IVF study.

XII. Safety Updates: Safety update submitted March 2, 2001 includes a summary table integrating adverse events reported in protocols 99-03, 99-04, and 99-05. This table contains errors which were subsequently corrected.

Safety update submitted June 14, 2001 consists of a single table entitled "Patients with Adverse Events" which corrects discrepancies that appeared in the summary table submitted March 2, 2001. This table is identical to that in revised draft labeling

submitted June 8, 2001. The table now correctly represents all adverse events observed in protocols 99-03, 99-04 and 99-05.

No new clinical data is submitted.

No long-term effects of treatment with Bravelle™ have been reported.

No new safety concerns are apparent.

Bravelle™ continues to be well-tolerated and safe when administered at the recommended dosages.

The benefit-to-risk ratio is favorable.

The benefits of the drug outweigh its risks.

XIII. Labeling: Revised draft labeling was submitted June 8, 2001 which incorporates most of the recommended revisions made by FDA to the applicant in a letter dated June 5, 2001.

In addition, the applicant proposed that the chemical name be changed from purified urofollitropin to [redacted] This proposed new name is not acceptable to FDA.

Two major recommended revisions have not been made:

A. [redacted]

B. [redacted]

The applicant will be asked to make the above mentioned major revisions as well as several other minor revisions and corrections.

Ridgely C. Bennett, M.D., M.P.H.

Medical Officer, HFD-580

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ridgely C. Bennett
7/27/01 08:33:13 AM
MEDICAL OFFICER

Shelley Slaughter
7/27/01 10:38:44 AM
MEDICAL OFFICER
I concur. See also Medical Team Leader Memo

APPEARS THIS WAY
ON ORIGINAL

For safety update see Medical Officer's review page 33.

NDA 21-289

Sponsor requested a pediatric waiver. A Pediatric Information Page will be completed upon approval of the application.

/s/

Paul Stinavage
1/18/01 10:38:11 AM
MICROBIOLOGIST
Product manufacture at SP Pharmaceuticals, Albuquerque, NM. Lyophilize
d drug product.

David Hussong
1/18/01 01:35:07 PM
MICROBIOLOGIST

APPEARS THIS WAY
ON ORIGINAL