# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-484

# Clinical Pharmacology and Biopharmaceutics Review

# Office of Clinical Pharmacology and Biopharmaceutics

*New Drug Application Filing and Review Form*

General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| NDA Number | 21-289 | Brand Name | Bravelle |
| OCPB Division I | HFD-870 | Generic Name | Urofollitropin/FSH |
| Medical Division | HFD-580 | Drug Class | Hormone |
| OCPB Reviewer | Sayed Al-Habet, Ph.D. | Indication(s) | Induction of Ovulation |
| OCPB Team Leader | Ameeta Parekh, Ph.D. | Dosage Form | Injection (SC or IM) |
| | | Dosing Regimen | 150-450 IU X 12 days |
| Date of Submission | September 28, 2001 | Route of Administration | SC or IM |
| Estimated Due Date of OCPB Review | July 13, 2001 | Sponsor | Ferring Pharmaceuticals |
| PDUFA Due Date | September 28, 2001 | Priority Classification | 3S |
| Division Due Date | July 29, 2001 | | |

Clin. Pharm. and Biopharm. Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments if any |
|---|---|---|---|---|
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | X | | | |
| HPK Summary | X | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | X | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| *Healthy Volunteers-* | | | | |
| single dose: | X | 1 | | |
| multiple dose: | X | 1 | | |
| Patients- | | | | |
| single dose: | X | 1 | | |
| multiple dose: | X | 1 | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | X | 1 | | |
| fasting / non-fasting multiple dose: | X | 1 | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD: | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD: | | | | |
| Phase 1 and/or 2, proof of concept: | X | 1 | | |
| Phase 3 clinical trial: | X | 1 | | |

| | | | | |
|---|---|---|---|---|
| **Population Analyses -** | | | | |
| Data rich: | NO | 1 | | |
| Data sparse: | No | 1 | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | X | 1 | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **5** | | |
| | | | | |

| **Filability and QBR comments** | | |
|---|---|---|
| | **"X" if yes** | **Comments** |
| **Application filable ?** | | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? |
| **Comments sent to firm ?** | | Comments have been sent to firm (or attachment included). FDA letter date if applicable. |
| **QBR questions (key issues to be considered)** | | |
| **Other comments or information not included above** | | |
| **Primary reviewer Signature and Date** | **Sayed Al-Habet, Ph.D.** | |
| **Secondary reviewer Signature and Date** | **Ameeta Parekh, Ph.D.** | |

CC: NDA 21-289, HFD-850 (p. Lee), HFD-580 (Spell-LeSane), HFD-870 (Al-Habet, Parekh, Malinowski, Hunt), CDR (B. Murphy, biopharm file)

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
# (FINAL VERSION May 30, 2001)

| | |
|---|---|
| NDAs: 21-289<br>Category: 3S | Submission Date:<br>September 28, 2000<br>March 1, 2001<br>April 3, 2001 |

| | |
|---|---|
| **Generic Name:** | Urofollitropin for injection<br>(Follicle Stimulating Hormone or FSH) |
| **Brand Name:** | BRAVELLE™ |
| **Formulations:** | 75 IU of FSH powder with accompanying vial of sterile diluent containing 2 ml of 0.9% sodium chloride for injection |
| **Route of Administration:** | Subcutaneous or Intramuscular |
| **Indication:** | Induction of ovulation/Controlled Ovarian Stimulation |
| **Sponsor:** | Ferring Pharmaceuticals, Inc.<br>Tarrytown, New York |
| **Type of Submission:** | NDA |
| **Reviewer:** | Sayed Al-Habet, Ph.D. |

**Dates of Review:**

| | |
|---|---|
| Received for Review: | March 14, 2001 |
| First Draft: | May 1, 2001 |
| Revised Draft: | May 8, 2001 |
| Final Draft | May 14, 2001 |
| Final Review | May 22, 2001 |

# TABLE OF CONTENTS

## Synopsis:

Bravelle™ is a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. Human FSH consists of two non-covalently linked glycoproteins designated as the α and β subunits. Bravelle™ contains 1– 2 % luteinizing hormone (LH) activity based on bioassay. Human Chorionic Gonadotropin (hCG) is not detected in Bravelle ™. Bravelle ™ in conjunction with Human Chorionic Gonadotropin (hCG) is indicated for multiple follicular development controlled ovarian stimulation and ovulation induction in patients who have previously received pituitary suppression.

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. The maximum daily dose of Bravelle ™ should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended. Bravelle ™ is administered by subcutaneous or intramuscular injection.

Each vial of Bravelle ™ contains 75 International Units (IU) of follicle stimulating hormone (FSH) activity, plus 20 mg of lactose as the monohydrate and 0.005 mg Tween in a sterile, lyophilized form. The final product contains sodium phosphate buffer (sodium phosphate tribasic and phosphoric acid).

## GENERAL COMMENTS:

1. It should be noted that in study # 99-02 two different doses were administered for single dose (225 IU) and multiple dose (150 IU).

2. The mean Cmax following a single dose of 225 IU is 5.9 and 7.0 mIU/ml after SC and IM, respectively. After a multiple injection for 7 days of 150 IU, the Cmax was 14.8 and 11.5 mIU/ml for SC and IM respectively.

3. Without the knowledge of the absolute bioavailability of FSH following SC or IM, the data reported for clearance and volume of distribution should be considered as "apparent".

4. No data is available in patients with renal or hepatic impairment

5. No data is available related to drug-drug interactions.

6. No data is available related to the metabolism and/or metabolic fate of FSH.

7. FSH is derived from the urine of postmenopausal women. Therefore, precautions should be taken to ensure that the drug is safe and free from infectious pathogens,

especially HIV.

8. It should be noted that the urine will be collected outside the US by an independent supplier named [redacted] The latest inspection report on this institute to specifically ensure the safety, quality of urine, and GMP compliance should be checked.

**The following comments, among other things, were conveyed to the sponsor during the teleconference held on March 26, 2001.**

9. It is important to note that the mean Cmax following a single dose of 225 IU is 5.9 and 7.0 mIU/ml after SC and IM, respectively. By contrast, after a multiple injection for 7 days of a smaller dose of 150 IU, the Cmax was 14.8 and 11.5 mIU/ml for SC and IM respectively. The reason for this could be due to drug accumulation.

10. In labeling, please replace the heading [redacted] with "Elimination"

11. In labeling, the reported half lives under heading of [redacted] should be consistent with the data reported in the PK summary Table.

12. In labeling, the legend of the PK summary Table should refer to the data as Mean ±SD.

13. In labeling, the data in the PK summary Table should be consistent with the data shown in the final PK report. All data should be based on a descriptive statistics. In addition, all data derived from EM algorithm should be omitted as this causing great deal of confusion. The Agency is interested in "one set" of reliable and consistent data throughout.

14. Unless we know the absolute bioavailability of the drug after SC and IM, the clearance and volume of distribution should be referred to as "apparent" parameters.

In the absence of absolute bioavailability of the drug, the focus of the PK report is on the following parameters: Cmax, Tmax, AUC $_{(0-\infty}$, Ka, and half life.

## RECOMMENDATION

Based on the information submitted, this NDA is ACCEPTABLE to the Office of Clinical Pharmacology and Biopharmaceutics. Labeling is currently under review.

# Executive Summary

**Background:**

Bravelle™ is a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. Bravelle ™ in conjunction with Human Chorionic Gonadotropin (hCG) is indicated for multiple follicular development controlled ovarian stimulation and ovulation induction in patients who have previously received pituitary suppression.

The recommended initial dose of Bravelle ™ for ovulation induction in patients who have received GnRH agonist or antagonist pituitary suppression is 150 IU daily for the first 5 days of treatment. However, the recommended initial dose for Assisted Reproductive Technology-ART (i.e., patients undergoing *in vitro* fertilization) is 225 IU for 5 days. The maximum daily dose of Bravelle ™ in either conditions should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended. Bravelle ™ is administered by subcutaneous or intramuscular injection.

**Clinical Pharmacology and Pharmacokinetics Studies:**

Following a single dose of 225 IU of Bravelle administered subcutaneously (SC) or intramuscularly (IM), the drug is slowly absorbed from the site of injection with mean Tmax occurring between 18 to 21 hours. However, following a multiple dose injection of 150 IU for 7 days, the Tmax attained more rapidly, between 10 to 11 hours. The mean Cmax following a single dose of 225 IU is 5.9 and 7.0 mIU/ml after SC and IM, respectively. After a multiple injection for 7 days of a smaller dose of 150 IU, the Cmax was 14.8 and 11.5 mIU/ml for SC and IM respectively. Overall, the SC administration appears to give a higher FSH level. Depending on the method of calculation, the half-life after a single dose appears to be longer (~35-40 hours) than after multiple dosing (~15-25 hours) for both SC and IM.

Based on a two controlled clinical studies (#99-03 and 04) SC administration appears to achieve a slightly higher ovulation, oocytes retrieval, and pregnancy rates. Briefly, patients received 150 to 450 IU SC or IM of Bravelle or Follistim SC for 12 days. Follistim is a marketed FSH from rDNA. The % ovulation was 96.2%, 92.9%, and 85.7% and the pregnancy rate was 25%,18.9%, and 26.3% for SC, IM, and Follistim SC, respectively. The mean number of oocytes retrieved was 14.3, 13.1, and 13.6 for SC, I M, and Follistim, respectively.

From both clinical studies the data is somewhat in good agreement with the PK data in which SC administration appears to provide a higher level of FSH serum levels than IM. The choice of the route of administration may depend on the patient's preference.

# SUMMARY REVIEW
# OF PHARMACOKINETICS AND BIOAVAILABILITY
# (Question Based Review, QBR)

## A) BACKGROUND:

**What are the Physico-Chemical Properties of Bravelle?**

FSH and LH belong to a family of glycoprotein hormone. Each of these hormones is a heterodimer composed of two non-covalently associated subunits. The α-subunit is common to both hormones; it contains 92 amino acids and two N-linked oligosaccharide side chains. The α-subunit contains cysteine residues that form five disulfide bonds which help maintain the structure of the subunit. The α-subunit is inactive.

The β-subunit is unique to each hormone and also includes two N-linked oligosaccharide side chains. The FSH β-subunit consists of 111 amino acids and 12 cysteine residues that form six disulfide bonds. The β-subunit determines the biological activity of FSH, and, like the α-subunit, is not biologically active by itself. The two subunits combine by non-covalent means to form the active glycoprotein hormone.

**What is the Source of Raw Materials?**

The initial source of the drug substance, the urine of menopausal and postmenopausal women. This will be collected a pool of donors by ——— ——— The system is dependent on the good will of the donors who are not paid for their donations. The collected urine undergoes ——— process at this . — The final products are manufactured by SP Pharmaceuticals in Albuquerque, New Mexico.

**What is the History of Product Batch?**

A total of five production batches ranging from ——— vials were produced. Batches FMA 001 to 004 are considered primary stability batches. The vials from Lot FMA 001 were used in the clinical trials FPI FSH 99-02 (PK, FSH 9903 (OI) and FSH 99-04 (IVF). Batch FMA 005 was used for transfer of technology and for the Phase IIB clinical trails FPI-FSH-2000-04 and FSH-200-05. There was no change in the formulation throughout the clinical program. Therefore, the clinical formulation is the final formulation that to be marketed.

**What are the Indications of Bravelle?**

Bravelle ™ in conjunction with hCG, is indicated for multiple follicular development

(controlled ovarian stimulation) and ovulation induction in patients who have previously received pituitary suppression.

**What is the Mechanism of Action of Bravelle?**

Bravelle administration for 7 to 12 days stimulates follicular growth and maturation. When sufficient follicular maturation has occurred, hCG must be given to induce ovulation.

**How Will Bravelle be Supplied (Formulation)?**

Bravelle ™ (purified urofollitropin for injection, USP) will be available in vials as a sterile, lyophilized, white to off-white powder — Each vial contains 75 IU of FSH and is accompanyed with a vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP.

The drug will be manufactured by SP Pharmaceuticals, Inc., Albuquerque, New Mexico for Ferring Pharmaceuticals Inc., Tarrytown, New York,

**What is the Proposed Dosage and Administration of Bravelle?**

**Infertile patients with oligo-anovulation:** The dose of Bravelle ™ to stimulate development of ovarian follicles must be individualized for each patient.
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 ™. Patients should be followed closely for at least 2 weeks after hCG administration.

**Assisted Reproductive Technologies:** The recommended initial dose of Bravelle ™ for patients who have received GnRH agonist or antagonist pituitary suppression 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. 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 to induce final follicular maturation in preparation for oocyte retrieval.

**What Assay Method Was Used?**

The FSH plasma concentration was determined by ——— assay. The lower limit of quantitation was — mIU/ml with a CV of <20%. The working range of calibration curve range from . — mIU/ml. The inter-assay precision measured as the %CV ranged from 3.64% to 10.3 and the intra-assay precision ranged from 1.16%to 4.55%. The percent accuracy ranged from 86.7% to 102%.

## B) CLINICAL PHARMACOLOGY STUDIES:

**What is the Bioavailability of Bravelle ?**

The absolute baioavailability of Bravelle following subscutaneous or intramuscular administration is unknown. Therefore, we have no information on the degradation, breakdown and/or metabolism of FSH during the absorption process from the site of injection. However, a study was conducted after SC and IM injections to determine the bioavailability relative to each route of administration (study # FPI FSH 99-02).

Briefly, this was open-label, single center study in 28 evaluable normal pre-menopausal down regulated female subjects. There were two treatment groups consisting of 16 subjects given single and multiple doses of purified FSH SC and 12 different subjects given single and multiple doses of purified FSH IM. Following a single dose of 225 IU of purified FSH SC and IM serum was collected at 0 (pre-dose),1, 2, 4, 6, 8, 10, 12, 16, 24 ,30, 36, 48, 72, 96, and 120 hours. Seven days later, subjects in each group received 7 daily doses of purified FSH (150 IU qd) SC or IM (always the same route of administration as the single dose). Serum was collected immediately prior to each daily dose. After the seventh and final dose serum specimens were collected at 1, 2, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, and 72 hours.

A summary of the data is shown in Table 1 and Figures 1 and 2. From the data, it can be seen that the serum level of FSH after SC is higher than after IM following a single and multiple doses. In addition, it appears that the data after SC administration are less variable than after IM. The mean Cmax and AUC after SC was approximately 15% to 30% higher than after IM administration of single and multiple doses. The half-life after multiple dose administration appears to be shorter (~20-25 hours) than after single dose (~35 to 40 hours). It should be noted that there was some inconsistency in reporting some of the data, particularly, for the half-life. These were discussed with the sponsor in the teleconference held in March 26, 2001.

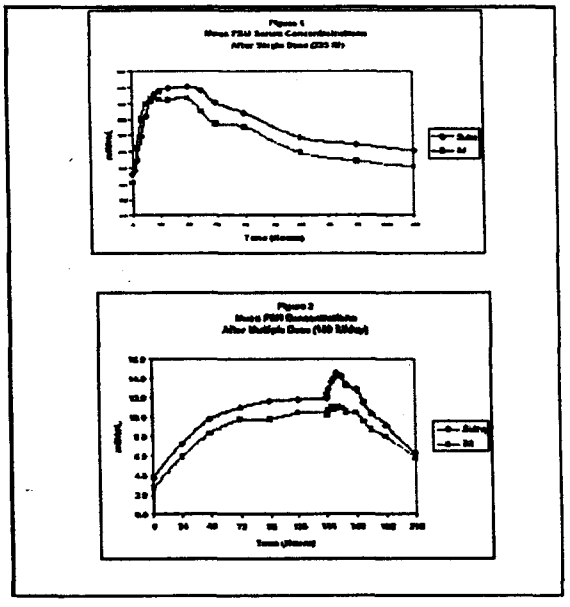
Overall, based on the available PK data, SC appears to provide slightly higher AUC and Cmax.

**Table 1: Summary of the Pharmacokinetic Parameters of FSH After SC or IM Single Dose (225 IU) and Multiple Dose (150 IU) Administration**

| Parameters | Single Dose SC (255 IU) | | | Single Dose IM (255 IU) | | |
|---|---|---|---|---|---|---|
| | Mean | SD | % CV | Mean | SD | % CV |
| Cmax (mIU/ml) | 6.025 | 1.73 | 28.7 | 7 | 4 | 57.7 |
| Tmax (h) | 21.3 | 7.4 | 35 | 17.8 | 12.6 | 70.4 |
| AUC(obs) mIU.h/ml) | 379.3 | 109.7 | 28.6 | 343.4 | 162 | 47.2 |
| Half Life (h) | 42.9 | 18.5 | 43.1 | 43.3 | 27.9 | 64.5 |
| Ka ($h^{-1}$) | 0.09103 | 0.03892 | 42.8 | 0.17626 | 0.20512 | 116.4 |

| Parameters | Multiple Dose SC (150 IU) | | | Multiple Dose IM (150 IU) | | |
|---|---|---|---|---|---|---|
| | Mean | SD | % CV | Mean | SD | % CV |
| Cmax (mIU/ml) | 14.8 | 2.9 | 19.5 | 11.5 | 2.9 | 25.2 |
| Tmax (h) | 9.6 | 2.1 | 21.8 | 11.3 | 8.4 | 74.3 |
| $AUC_{(0-24)}$ mIU.h/ml) | 234.7 | 77.0 | 32.9 | 192.1 | 52.3 | 27.0 |
| Half Life (h) | 24.8 | 10.7 | 43.0 | 24.4 | 13.4 | 55.0 |
| Ka ($h^{-1}$) | 0.10819 | 0.0542 | 50.1 | 0.05937 | 0.03054 | 51.4 |

**Figures 1 and 2 show the mean FSH plasma concentration-time profiles after SC and IM injections.**



**What is the PK Relationship with Dose (i.e., is there dose proportionality)?**

The sponsor has conducted a population pharmmacokinetics study in a limited number of patients (n=16) after 375 and 450 IU given as IM or SC as shown below:

- n= 5 for 300 mg IM
- n= 5 for 375 mg IM
- n= 2 for 450 mg IM
- n= 3 for 375 mg SC
- n= 4 for 450 mg SC

The sponsor has focused only on clearance (CL) and volume of distribution (Vd) data. As indicated above, these parameters are somewhat irrelevant in the absence of the absolute bioavailability data. The sponsor claimed that the drug may follow a linear (dose proportional) PK as the CL and Vd did not change with dose. The study and the analysis lack adequate power (n=16) and number of patients at each dose level is too small to conclusively conclude dose proportionality. The mean ± SD of clearance and volume of distribution from the population PK analysis and study # 99-09 are shown in Tables 2 and 3.

**Table 2: Apparent Clearance and Volume of distribution Based on Poplulation PK Analysis (n=16)**

| Parameter | IM | | | SC | | |
|---|---|---|---|---|---|---|
| | Mean | SD | %CV | Mean | SD | %CV |
| Clearance (ml/h) | 669.67 | 151.2 | 22.59 | 605.70 | 254.7 | 42.05 |
| Volume (ml) | 37,163 | 13,609 | 36.62 | 27,121 | 4602 | 16.97 |

**Table 3: Apparent Clearance and Volume of distribution Based on study # 99-02 (see above)**

| Parameter | IM (150 IU multiple dose) | | | SC (150 IU multiple dose) | | |
|---|---|---|---|---|---|---|
| | Mean | SD | %CV | Mean | SD | %CV |
| Clearance (ml/h) | 759.3 | 176.7 | 23.3 | 711.1 | 329.7 | 46.4 |
| Volume (ml) | 16,601.9 | 4296.7 | 25.8 | 21,168.8 | 3151.1 | 14.8 |

From the above Tables it can be seen that overall the data derived from the population PK analysis are somewhat comparable to the data derived from the classical PK study (#99-02). One exception is that the volume of distribution after IM derived from the population analysis is about twice larger than that of the classical PK study.

**Is There any PK/PD Relationship With Bravelle?**
**(Controlled Clinical Trial)**

Two pivotal controlled clinical studies were conducted comparing SC or IM administration of Bravelle to SC Follistim. In the first study (# 99-03), patients received 150 IU SC or IM of Bravelle for 5 days followed by individualized dosing to a maximum of 450 IU qd for a total duration not exceeding 12 days. The total number of patients was 36 for SC and 37 for IM. The third arm of the study was in 38 patients with Follistim administered SC. Follistim is a marketed FSH manufactured by recombinant DNA (rDNA). From this study the % ovulation in the Primary Efficacy Responders was 96.2%, 92.9%, and 85.7% for SC, IM, and Follistim SC, respectively (Figure 3). The same trend for a favorable response for SC administration is also observed in the Intent-to-Treat Group of patients (Figure 4). The continuing pregnancy rate in Intent-to-Treat group based on ultrasound monitoring was 25%, 18.9%, and 26.3% for SC, IM, and Follistim SC, respectively (Figure 5). These data are somewhat in good agreement with the PK data in which SC administration appears to show higher level of FSH serum levels than IM. Therefore, based on this study SC administration of Bravelle is preferable over IM.

**Figure 3. Percentage of Patients Ovulating following SC or IM Bravelle or SC Folistim in Primary Efficacy Responders Group (study # 03).**

| Primary Efficacy Variable – Percentage of Patients Ovulating<br>Primary Efficacy Responders | | | | |
|---|---|---|---|---|
| | FSH SC | FSH IM | Follistim® SC | p-value |
| Parameter | N=26 | N=28 | N=35 | |
| Ovulation (%) | 25 (96.2) | 26 (92.9) | 30 (85.7) | 0.340 |

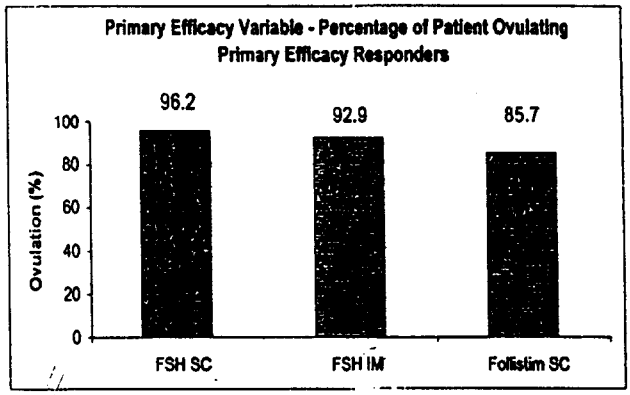



**Figure 4. Percentage of Patients Ovulating following SC or IM Bravelle or SC Folistim in Intent-to-Treat Group (study # 03)**

| Primary Efficacy Variable – Percentage of Patients Ovulating<br>Intent-To-Treat | | | | |
|---|---|---|---|---|
| | FSH SC | FSH IM | Follistim® SC | p-value |
| Parameter | N=36 | N=37 | N=38 | |
| Ovulation (%) | 25 (69.4) | 26 (70.3) | 30 (78.9) | 0.591 |

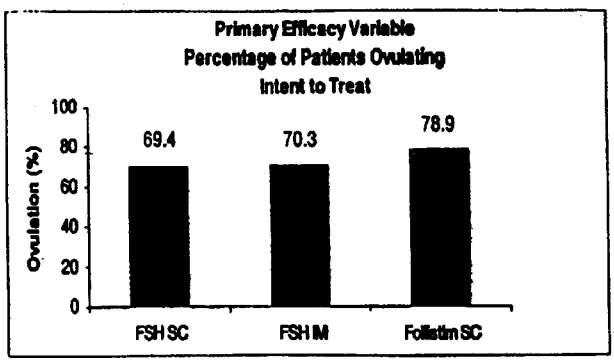
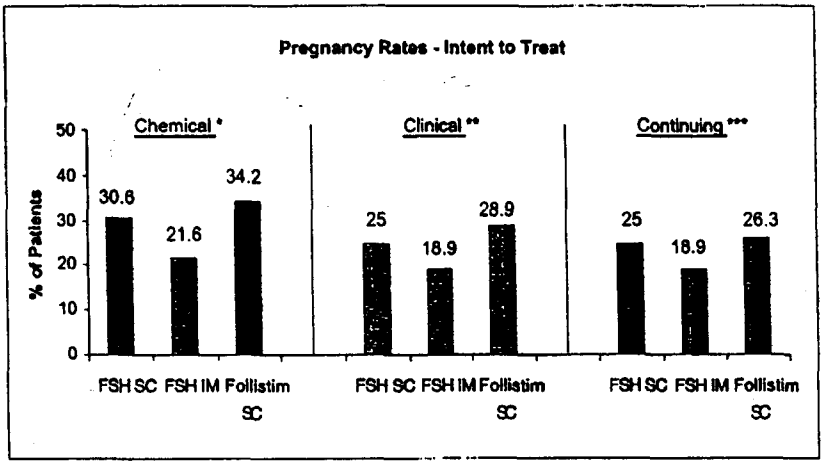


**Figure 5. Efficacy Variables and Pregnancy rates following SC or IM Bravelle or SC Follistim in Intent-To-Treat Group (study # 03)**

| Secondary Efficacy Variables Intent-To-Treat | | | | |
|---|---|---|---|---|
| | FSH SC | FSH IM | Follistim® SC | p-value |
| Parameter | N=36 | N=37 | N=38 | |
| Met hCG Criteria (%) | 29 (80.6) | 29 (78.4) | 37 (97.4) | 0.037* |
| Received hCG (%) | 26 (72.2) | 28 (75.7) | 35 (92.1) | 0.070+ |
| No. of Follicles Meeting hCG Criteria (%) | 140 | 128 | 184 | |
| Mean Peak Serum $E_2$ (pg/mL) Levels (SD) | 990.9 (676.2) | 893.2 (815.2) | 1109.0 (788.9) | 0.474 |
| Chemical Pregnancy (%) | 11 (30.6) | 8 (21.6) | 13 (34.2) | 0.466 |
| Clinical Pregnancy (%) | 9 (25.0) | 7 (18.9) | 11 (28.9) | 0.595 |
| Continuing Pregnancy (%) | 9 (25.0) | 7 (18.9) | 10 (26.3) | 0.724 |

* p = 0.020 for purified FSH SC vs. Follistim®SC, p = 0.011 for purified FSH IM vs. Follistim®SC.
+ p= 0.025 for purified FSH SC vs. Follistim®SC, p=0.052 for purified FSH IM vs. Follistim ®SC.




* Positive βhCG
** Ultrasound showing intrauterine sac and fetal heart motion
*** Ultrasound showing intrauterine sac and fetal heart motion on last evaluation

The second study (#99-04) was conducted in patients undergoing *In Vitro* Fertilization. Briefly, each patient was down regulated with daily injections of leuprolide of 0.5 mg SC (up to 20 days) commencing 7 days before the anticipated onset of menses. The initial dose of the assigned follitropin was 225 IU for 5 days given SC or IM and then individually titrated up to a maximum of 450 IU for a total duration not to exceed 12 days. The total number patients completed the study was 177 (n=60 for SC, n=59 for IM. and n=58 for Follistim SC group).

The summary of the results is shown in Figures 6-10. In the Primary Efficacy responders Group, the mean number of oocytes retrieved was 14.3, 13.1, and 13.6 for SC, I M, and Follistim group, respectively (Figure 6). The same trend was observed in the Intent-to-Treat Group (Figure 7). The percentage of patients continued pregnancy in Intent-To-Treat group was 41.7%, 32.2%, and 29.3% in SC, IM, and Follistim group, respectively (Figure 8). A similar trend was seen in Primary Efficacy Responders which was 25%, 19%, and 17% in SC, IM, and Follistim, respectively. As in study # 03, it can be concluded that SC is the preferable route of administration of Bravelle.

**Figure 6. Mean Number of Oocytes Retrieved following SC or IM Bravelle or SC Follistim in Primary Efficacy Responders Group (Study # 04)**

| Primary Efficacy Variable – Mean Number of Oocytes Retrieved Primary Responders (Received hCG) | | | | | | |
|---|---|---|---|---|---|---|
| | FSH SC | FSH IM | Follistim® SC | p-value | | |
| Parameter | N=56 | N=55 | N=56 | FSH SC vs. Follistim® | FSH IM vs. Follistim® | FSH SC vs. FSH IM |
| Total oocytes retrieved (SD) | 14.3 (± 7.3) | 13.1 (± 7.3) | 13.6 (± 8.5) | 0.626 | 0.725 | 0.403 |
| Mature oocytes retrieved (SD) | 10.6 (± 5.2) | 9.4 (± 5.1) | 9.9 (± 5.4) | 0.495 | 0.621 | 0.241 |

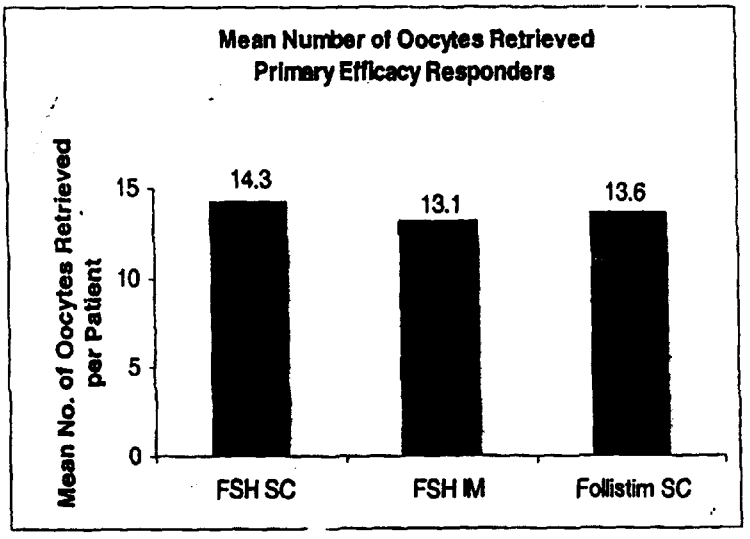


**Figure 7. Mean Number of Oocytes Retrieved following SC or IM Bravelle or SC Follistim in Intent-to-Treat Group (Study # 04)**

| Primary Efficacy Variable – Mean Number of Oocytes Retrieved Intent to Treat | | | | | | |
|---|---|---|---|---|---|---|
| | FSH SC | FSH IM | Follistim® SC | p-value | | |
| Parameter | N=60 | N=59 | N=58 | FSH SC vs. Follistim® | FSH IM vs. Follistim® | FSH SC vs. FSH IM |
| Total oocytes retrieved (SD) | 13.3 (± 7.9) | 12.2 (± 7.8) | 13.1 (± 8.7) | 0.879 | 0.537 | 0.438 |
| Mature oocytes retrieved (SD) | 9.9 (± 5.7) | 8.7 (± 5.5) | 9.5 (± 5.6) | 0.760 | 0.447 | 0.283 |

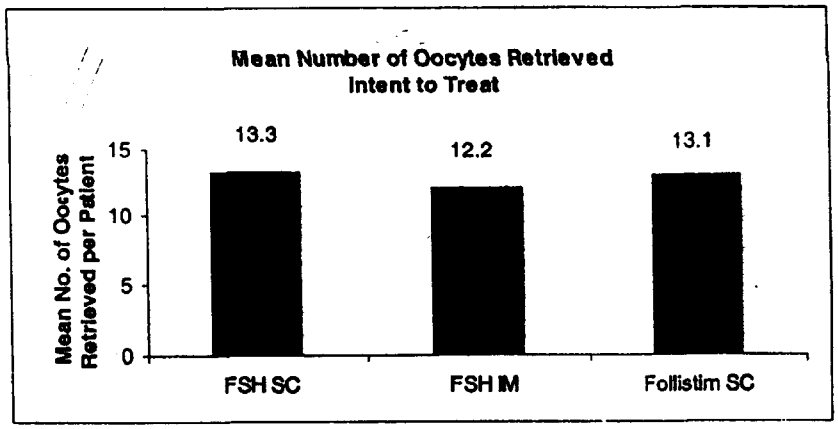
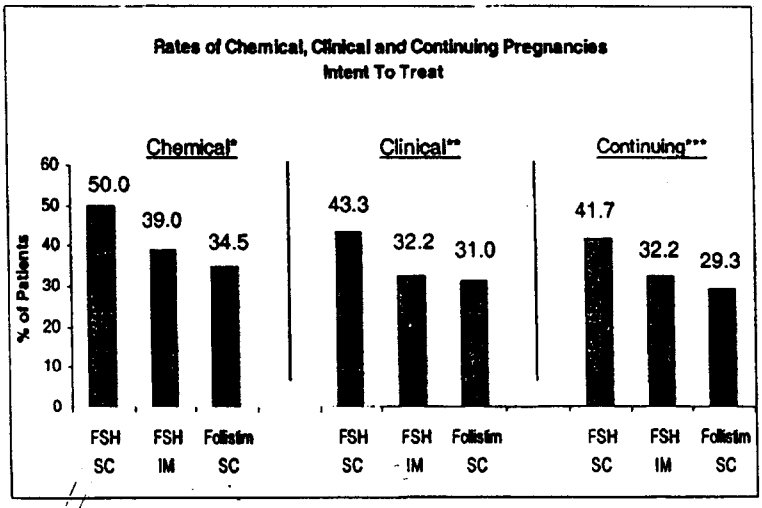


**Figure 8. Mean Rates of Pregnancies following SC or IM Bravelle or SC Follistim (Study # 04)**




* Positive βhCG
** Ultrasound showing intrauterine sac and fetal heart motion
*** Ultrasound showing intrauterine sac and fetal heart motion on last evaluation

| Secondary Efficacy Variables – Primary Efficacy Responders | | | | | | |
|---|---|---|---|---|---|---|
| | FSH SC | FSH IM | Follistim® SC | p-value | | |
| Parameter | N=56 | N=55 | N=56 | FSH SC vs. Follistim® | FSH IM vs. Follistim® | FSH SC vs. FSH IM |
| Pts. With embryo transfer (%) | 54 (96.4) | 51(92.7) | 55(98.2) | 0.558 | 0.163 | 0.389 |
| Pts. With chemical pregnancy (%) | 30(53.6) | 23(41.8) | 20(35.7) | 0.057 | 0.509 | 0.215 |
| Pts. With clinical pregnancy (%) | 26(46.4) | 19(34.5) | 18(32.1) | 0.122 | 0.788 | 0.202 |
| Pts. With continuing pregnancy (%) | 25(44.6) | 19(34.5) | 17(30.4) | 0.118 | 0.637 | 0.277 |

**The following list of studies were not conducted by the sponsor:**

1. Elimination Pathways (Metabolism and Excretion)
2. Identification of the Active metabolites, if any.
3. Plasma Protein Binding
4. Special Populations.
    - Hepatic Disease
    - Renal Disease
5. Drug-drug interaction

**ClinPharm/Biopharm Briefing on: June 22, 2001.**

**Briefing Attendees:** Drs. Ridgely Bennet, Dornette Spell-LeSane, Martin Haber, John Hunt, Ameeta Parekh, and Sayed Al- Habet

Reviewed by:

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD/FT initialed by Ameeta Parekh, Ph.D. _____

cc: NDAs # 21-289: HFD-580, HFD-860 (Al-Habet, Parekh, and Malinowski), and Drug files (Biopharm File, CDR).

# Appendix I

## Sponsor's Proposed Label

13 pages redacted from this section of the approval package consisted of draft labeling

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

/s/

Sayed Al-Habet
12/3/02 02:59:02 PM
BIOPHARMACEUTICS

Venkateswar Jarugula
12/3/02 03:35:12 PM
BIOPHARMACEUTICS

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
# (DFS Version December 3, 2002)

NDAs: 21-484
Category: 3S

Submission Date:
February 15, 2002
July 25, 2002

| | |
|---|---|
| **Generic Name:** | Urofollitropin for injection<br>(Follicle Stimulating Hormone or FSH) |
| **Brand Name:** | BRAVELLE™ |
| **Formulations:** | 75 IU of FSH powder with accompanying vial of sterile diluent containing 2 ml of 0.9% sodium chloride for injection |
| **Route of Administration:** | Subcutaneous or Intramuscular |
| **Indication:** | Assisted Reproductive Technology/In Vitro Fertilization (ART/IVF) |
| **Sponsor:** | Ferring Pharmaceuticals, Inc.<br>Tarrytown, New York |
| **Type of Submission:** | NDA |
| **Reviewer:** | Sayed Al Habet, Ph.D. |
| **Dates of Review:** | |

| | |
|---|---|
| Received for Review: | February 25, 2002 |
| First Draft: | September 5, 2002 |
| Revised Draft: | September 9, 2002 |
| Final draft | November 7, 2002 |
| DFS Version | December 3, 2002 |

# Executive Summary

Bravelle™ is a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. Human FSH consists of two non-covalently linked glycoproteins designated as the α and β subunits. Bravelle™ contains 1– 2 % luteinizing hormone (LH) activity based on bioassay. Human Chorionic Gonadotropin (hCG) is not detected in Bravelle ™. Bravelle ™ in conjunction with Human Chorionic Gonadotropin (hCG) was recently approved for ovulation induction in patients who have previously received pituitary suppression (NDA # 21-289).

The sponsor has submitted this NDA for a new indication to induce ovulation and pregnancy in infertile women as part of Assisted Reproductive Technology and *In Vitro* Fertilization ART/IVF). It should be noted that this NDA was submitted to re-initiate the review of the *in vitro* fertilization (ART/IVF) clinical indication which was submitted in the original NDA #21-289. In the original NDA, ART/IVF indication was not approved due to lack of adequate efficacy (see Medical Officer's original review).

This NDA contains final study report for the second, controlled study following Bravelle subcutaneous (SC) and Follistim SC administration for ART/IVF indication (FPI FSH 2001-01). It should be noted that there was no intramuscular (IM) arm in this study for Bravelle. In addition, the sponsor did not provide adequate justification for IM administration for ART/IVF indication and no bioequivalency can be established for Bravelle between SC and IM routes (sponsor's letter dated July 25, 2002).

All information related to Clinical Pharmacology and Biopharmacetucs were crossed referenced to the original NDA #21-289. This information were reviewed and discussed within the Office of Clinical Pharmacology and Biopharmacetuics and the Clinical Division. At that time there were no PK related issues of clinical importance. The original NDA was approved for SC and IM administration for ovulation induction (see original review). In the original NDA there was one PK study (#99-02) and two clinical studies: one for ovulation induction (study #99-03) and one for ART/IVF (study #99-04). The two clinical studies had no PK related information.

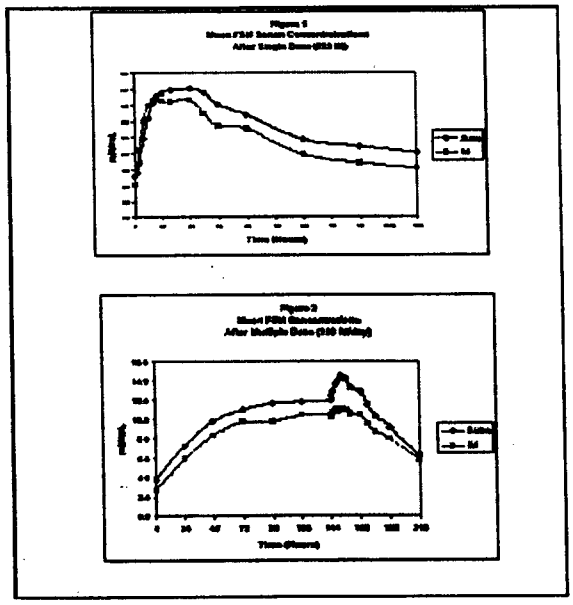
In terms of PK, study #02 was conducted in parallel groups of patients as single dose of 225 IU or multiple dose of 150 IU for 7 days administered either SC or IM. After the single dose, the FSH was slowly absorbed from the site of injection with mean Tmax occurring between 18 to 21 hours. However, following a multiple dose injections, the Tmax attained more rapidly, between 10 to 11 hours. The mean Cmax following a single dose was 5.9 and 7.0 mIU/ml after SC and IM, respectively. After the multiple injections, the mean Cmax was 14.8 and 11.5 mIU/ml for SC and IM respectively (**Table 1**). Overall, based on the mean data, the FSH serum levels after SC administration were approximately 10% and 22% higher than after IM injection for the single and multiple doses, respectively (**Table 1 and Figures 1 and 2**). These data indicate that the two routes of administration are not bioequivalent.

**Table 1: Summary of the Pharmacokinetic Parameters of FSH After SC or IM Single Dose (225 IU) and Multiple Dose (150 IU) Administration of Bravelle**

| Parameters | Single Dose SC (255 IU) | | | Single Dose IM (255 IU) | | |
|---|---|---|---|---|---|---|
| | Mean | SD | % CV | Mean | SD | % CV |
| Cmax (mIU/ml) | 6.025 | 1.73 | 28.7 | 7 | 4 | 57.7 |
| Tmax (h) | 21.3 | 7.4 | 35 | 17.8 | 12.6 | 70.4 |
| AUC(obs) mIU.h/ml) | 379.3 | 109.7 | 28.6 | 343.4 | 162 | 47.2 |
| Half Life (h) | 42.9 | 18.5 | 43.1 | 43.3 | 27.9 | 64.5 |
| Ka ($h^{-1}$) | 0.09103 | 0.03892 | 42.8 | 0.17626 | 0.20512 | 116.4 |

| Parameters | Multiple Dose SC (150 IU) | | | Multiple Dose IM (150 IU) | | |
|---|---|---|---|---|---|---|
| | Mean | SD | % CV | Mean | SD | % CV |
| Cmax (mIU/ml) | 14.8 | 2.9 | 19.5 | 11.5 | 2.9 | 25.2 |
| Tmax (h) | 9.6 | 2.1 | 21.8 | 11.3 | 8.4 | 74.3 |
| $AUC_{(0-24)}$ mIU.h/ml) | 234.7 | 77.0 | 32.9 | 192.1 | 52.3 | 27.0 |
| Half Life (h) | 24.8 | 10.7 | 43.0 | 24.4 | 13.4 | 55.0 |
| Ka ($h^{-1}$) | 0.10819 | 0.0542 | 50.1 | 0.05937 | 0.03054 | 51.4 |

**Figures 1 and 2 show the mean FSH plasma concentration-time profiles after SC and IM injections of Bravelle**



The objectives of the second IVF study (#2001-01) that was submitted in this NDA were:

1) To determine the efficacy SC Braville to SC Follistim (marketed FSH from rDNA).
2) To determine the safety and tolerance of Bravelle SC compared to Follistim SC.

This study is similar in the design to the previously reviewed study # 99-04 (see medical officer original review). Briefly, it was a randomized, parallel group study in women undergoing *in vitro* fertilization. Each patient was down regulated with daily injections of leuprolide of 0.5 mg SC (up to 20 days) commencing 7 days before the anticipated onset of menses. The initial dose of the assigned follitropin was 225 IU for 5 days given SC and then individually titrated up to a maximum of 450 IU for a total duration not to exceed 12 days. The total number of patients completed the study was 120 (n=60 for SC Bravelle and n=60 for Follistim SC). The clinical parameters after SC Bravelle and Follistim administration from this study are shown in **Figures 3-5**. From these data, it can be concluded that the number of oocyte retrieval after SC Bravelle and Follistim administration are similar (**Figures 3 and 4**, see also medical Officer review).

**Figure 3 (study # 2000-01):**

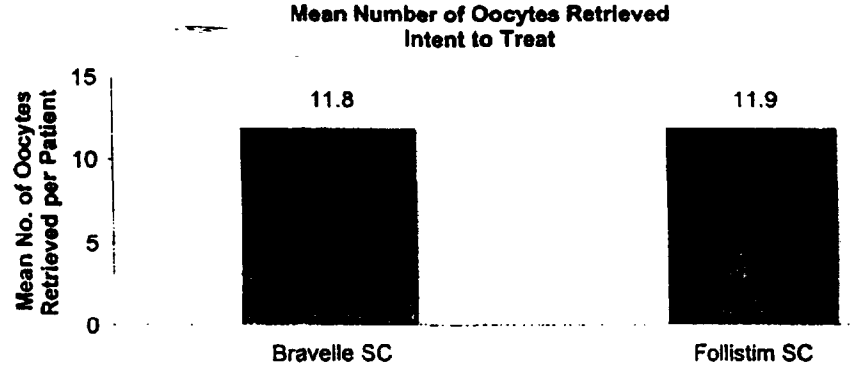



**Figure 4 (study # 2000-01):**

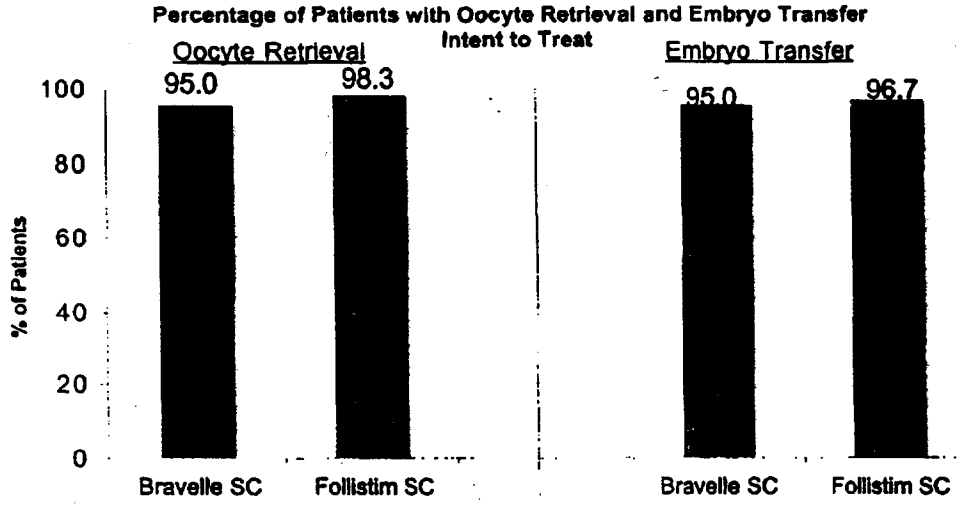
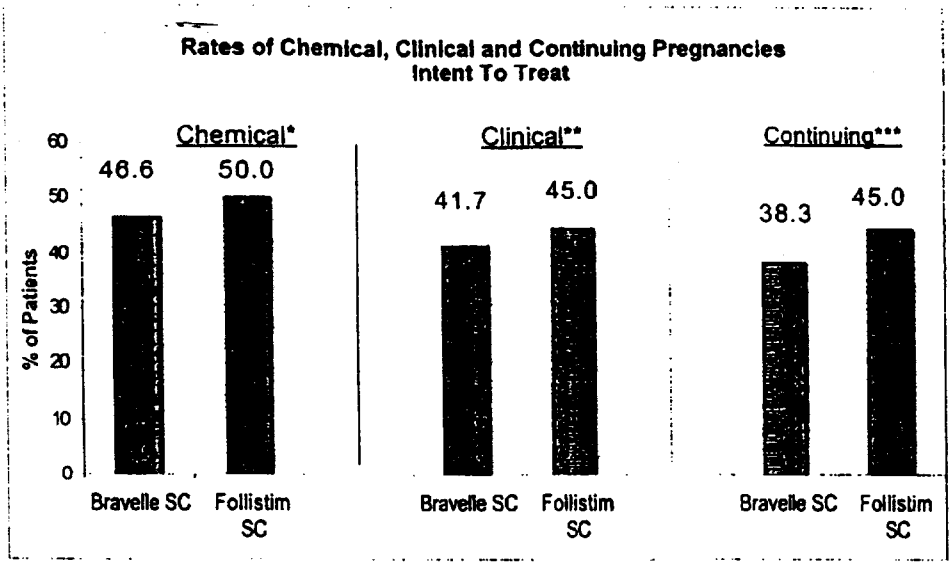


**Figure 5 (study # 2000-01):**




* Positive βhCG

** Ultrasound showing intrauterine sac

*** Ultrasound showing intrauterine sac and fetal heart motion on last evaluation

APPEARS THIS WAY
ON ORIGINAL

**Review Comments:**

Pivotal clinical study for IVF indication was conducted with SC administration of Bravelle and Follistim. No clinical data was obtained following IM administration of Bravelle for ART/IVF indication. However, the sponsor requested for approval of Bravelle for both SC and IM administration.

From the Clinical Pharmacology and Biopharmacetuics prespective, the lack of PK data to establish the bioequivalnce between SC and IM routes raises a major issue. The sponsor has not provided adequate justification for the use of IM administration of Bravelle. In addition, the sponsor has not provided justification for omitting IM arm in the ART/IVF study #01.

The PK data showed different FSH serum profiles after SC or IM administration (**Figures 1 and 2, study # 99-02**). The FSH serum levels after SC administration were approximately 10% and 22% higher than after IM injection for the single and multiple doses, respectively. These data indicate that the two routes of administration are not bioequivalent. According to the sponsor, this study was not designed to formally establish bioequivalence between the two routes of administration. It was mainly designed to compared the PK profiles after SC and IM administration (letter submitted July 25, 2002).

**Recommendation:**

From the Clinical Pharmacology and Biopharmaceutics point of view, SC administration only is recommended for ART/IVF indication. IM administration is not recommended based on the following:

1) The lack of safety and efficacy data following IM administration for ART/IVF indication.
2) The lack of data to establish bioequivalence between SC and IM administration.
3) The sponsor has not provided adequate justification for approval of IM administration without clinical data.
4) The serum levels of FSH after IM administration are consistently lower than after SC administration.

Briefing date: November 20, 2002

Briefing Attendees: Drs. Shelley Slaughter, Hank Malinowski, John Hunt, Ameeta Parekh, Venkat Jarugula, and Sayed Al Habet

Reviewed by:

Sayed Al Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD/FT initialed by Ameeta Parekh, Ph.D. _____