

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-149

MEDICAL REVIEW

Medical Officer's Original NDA Review

NDA Number: 21,149

Applicant: Serono Laboratories, Inc.
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Dates of Submissions: November 23, 1999 and January 13, 2000

Dates Received: November 24, 1999 and February 7, 2000

Date Review Completed: August 18, 2000

Date Review Finalized: September 1, 2000

I. General Information:A. Name of Drug:

1. Established Name: Choriogonadotropin alfa
2. Proprietary Name: Ovidrel
3. Chemical Name: Recombinant human chorionic gonadotropin

B. Pharmacologic Class: Human chorionic gonadotropinC. Proposed Indications: Induction of final follicular maturation and early luteinization in infertile women who have been appropriately pretreated with follicle stimulating hormone as part of an Assisted Reproductive Technology (ART) programD. Dosage Form: Lyophilized powder for injectionE. Route of Administration: SubcutaneouslyF. Strengths: 250 microgramsG. Dosage: 250 micrograms (equivalent to 5,000 USP units) one day following the last dose of the follicle stimulating

— Ovidrel should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography.

- H. Related Drugs: Chorionic gonadotropin, an extract of human urine, such as Profasi, Pregnyl, and A.P.L.
- II. Manufacturing Controls: Please refer to chemist's review for details
- III. Pharmacology: Please refer to pharmacologist's review for details
- IV. Clinical Background: Urinary-derived human chorionic gonadotropin has been used for more than 30 years to induce final follicular maturation and trigger ovulation in patients receiving gonadotropins for infertility therapy. It is an effective therapeutic analogue of LH. Recombinant hCG, being physico-chemically identical to native hCG would be anticipated to be clinically equivalent to urinary hCG in inducing final follicular maturation and ovulation in women undergoing ovulation induction, and to induce the necessary cellular changes that precede fertilization in women undergoing ART for treatment of infertility. Recombinant hCG will provide an alternative to urinary human chorionic gonadotropin. It is administered as a single injection during each treatment cycle.
- V. Regulatory Background:
- A. Ovidrel was investigated clinically in the United States under IND 48.934 submitted September 29, 1995.
- B. NDA 21,149 was presented at a Filing Meeting January 6, 2000 at which it was concluded that the application was filable for the ART indication, but could not be reviewed for the induction of ovulation indication until complete results from study 8209 were submitted.
- C. The applicant submitted the clinical trial report for study 8209 January 13, 2000.
- VI. Foreign Marketing History: Ovidrel is not approved for marketing in any foreign country.
- VII. Consultations: Please refer to response from Office of Post-Marketing Drug Risk Assessment.
- VIII. Clinical Studies: Three adequate and well-controlled phase III studies were designed to assess the safety and efficacy of recombinant hCG (Ovidrel) compared to urinary hCG (Profasi) for induction of final follicular maturation and ovulation in women undergoing ovulation induction with gonadotropins for ART or

oligo-anovulatory infertility. Two additional smaller supportive IVF/ET studies are ongoing in Australia and New Zealand. There are also three ongoing pilot studies in indications other than those of female infertility.

Study 7648, an IVF study which began in Europe and Israel in February 1995 and study 7927, an IVF study which began in the United States in February 1996 are pivotal IVF clinical trials. Study 8209, an ovulation induction study which began in Europe in March 1996 is the pivotal ovulation induction clinical trial. Studies 9073 and 9779 are smaller, supportive IVF clinical trials that are ongoing in Australia and New Zealand.

Studies 7648 and 7927 were prospective, randomized, multicenter trials which enrolled women undergoing a single cycle of superovulation and IVF/ET for treatment of infertility.

A. Study 7648:

"A phase III, double-blind, double-dummy, randomized multicenter study to compare the safety and efficacy of recombinant human chorionic gonadotropin (Ovidrel) with that of urinary human chorionic gonadotropin (Profasi) for inducing final follicular maturation and early luteinization in women undergoing superovulation with recombinant human follicle stimulating hormone (Gonal-F) prior to IVF/ET".

1. Investigators and Country:

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2. Objectives of the Study:

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The objectives of this study were to assess the safety and the

efficacy of r-hCG compared with u-hCG, both administered SC, for inducing final oocyte maturation and initiation of follicular luteinization in patients who had undergone pituitary desensitization and superovulation as part of an IVF/ET cycle. The primary objective was to compare the total number of oocytes retrieved per patient for patients who received either u-hCG or r-hCG and to show equivalence between u-hCG and r-hCG.

3. Rationale for the Study:

Treatment of subfertility and infertility by assisted reproductive technologies (ART) requires ovarian stimulation to increase the number of female gametes produced and the chance of a successful treatment outcome. Ovarian stimulation currently includes suppression of endogenous LH by administration of a gonadotropin releasing hormone agonist (GnRH-a) followed by stimulation of multiple follicular development by exogenous follicle stimulating hormone (FSH) administration. When adequate follicular development is reached, a single dose of human chorionic gonadotropin (hCG) is administered to mimic the endogenous LH surge and to achieve final follicular maturation. It has been documented that an inadequate LH/hCG surge in IVF leads to reduced egg recovery and a lower fertilization rate.

Profasi® (human chorionic gonadotropin) is a hormonal preparation extracted from the urine of pregnant women, which possesses luteinizing properties. The urinary source implies a number of disadvantages including lack of absolute source control, copurification of other urinary proteins, risk of immunological adverse reactions and a cumbersome collection procedure.

Recombinant human chorionic gonadotropin (r-hCG) is produced in genetically engineered Chinese Hamster Ovary (CHO) cells in which the genes encoding for the alpha and beta chains of human chorionic gonadotropin have been introduced through recombinant DNA technology. The advantages of producing hCG through recombinant DNA technology include high purity and specific activity, batch-to-batch consistency and independence from urine collection.

Recombinant human chorionic gonadotropin is being developed as a pharmaceutical product to replace the u-hCG (Profasi®).

4. Method of Assignment to Treatment:

When the follicular response to recombinant FSH (Gonal-F) was judged to be appropriate, the patient was randomized (in a blinded

fashion) to 1 of the following 2 regimens according to balanced blocks of 4 subjects, stratified by center:

- a SC injection of 250 μ g r-hCG (supplied in vials) and a sc injection of u-hCG placebo (supplied in ampules), or
- a SC injection of 5000 IU u-hCG (supplied in ampules) and a SC injection of r-hCG placebo (supplied in vials).

5. Number of Subjects:

A total of 205 subjects achieved down-regulation and were randomized to either r-hCG (104 subjects) or to u-hCG (101 subjects).

6. Duration of Clinical Trial:

One treatment cycle only (a single injection)

7. Inclusion Criteria:

- a. Infertility, defined as a woman desiring a pregnancy and having failed to conceive after at least 2 years of unprotected coitus. The couple's infertility could be attributable to any of the following causes:
 - tubal factor
 - mild endometriosis (American Fertility Society classification stage I or II)
 - unexplained causes (in this case, duration of infertility had to be at least three years).
- b. A male partner with semen analysis within the past 6 months showing acceptable values of semen, defined as $>10 \times 10^6$ spermatozoa/mL, $> 20\%$ with linear progression and a normal morphology as defined by the local laboratory, or an oocyte fertilization rate $\geq 50\%$ during any previous IVF attempt (if regular IVF had been performed only). Donor sperm (except in German centers) was acceptable if it met the criteria described above.
- c. Age 20-38 years
- d. Negative pregnancy test prior to beginning nafarelin therapy
- e. Regular spontaneous ovulatory menstrual cycles of 25-35 days
- f. During early follicular phase (Day 2-4), serum levels of the following

hormones assayed in the central laboratory within the ranges defined below:

- FSH \leq 12 IU/L
- LH \leq 13.5 IU/L
- PRL \leq 800 mIU/L
- T \leq 3.5 nmol/L

- g. No clinically significant abnormal hematology, chemistry or urinalysis according to central laboratory criteria
- h. Presence of both ovaries
- i. No more than 3 previous assisted conception cycles (GIFT, ZIFT, ICSI, SUZI and/or IVF)
- j. No treatment with clomiphene or gonadotrophins for at least 2 months prior to treatment in this study
- k. No assisted conception treatment for at least 2 full menstrual cycles
- l. Normal uterine cavity, as confirmed by either ultrasound scan, hysteroscopy, or hystero-graphy
- m. HIV negative
- n. Hepatitis B surface antigen (HbsAg) negative
- o. Willingness to participate and comply with the protocol for the duration of the study
- p. Signature on the Written Informed Consent Form

8. **Exclusion Criteria:**

- a. Clinically significant systemic disease (e.g. insulin-dependent diabetes, epilepsy, severe migraine, intermittent porphyria, hepatic, renal or cardiovascular disease, severe corticosteroid-dependent asthma)
- b. Any contraindication to being pregnant and/or carrying a pregnancy to term
- c. Extrauterine pregnancy in the past 3 months
- d. A body mass index greater than 30 kg/m²

- e. Polycystic ovarian syndrome (PCOS), defined by ultrasound as an ovary containing in 1 section at least 10 follicles, usually between 3 and 10 mm diameter
- f. Previous history of severe ovarian hyperstimulation syndrome
- g. Any medical condition which in the judgement of the Investigator and Sponsor could interfere with the absorption, distribution, metabolism or excretion of the drug
- h. Previous IVF or GIFT failure due to a problem of either sperm fertilization, or poor response to gonadotropin therapy. Poor responders were defined as women who matured ≤ 2 follicles in a previous attempt
- i. Abnormal gynecological bleeding of undetermined origin.
- j. Previous history of intolerance of FSH, GnRH agonists or hCG
- k. Simultaneous participation in another clinical trial
- l. Active substance abuse (e.g. smokers consuming more than 20 cigarettes/day)
- m. Refusal or inability to comply with protocol
- n. For the male partner, obvious leucospermia ($> 2 \times 10^6/\text{mL}$) or significant bacterial infection detected in semen analysis within the last 2 months

9. Trial Period:

February 1995-October 1996

10. Dosage and Mode of Administration:

Eligible patients received 400 μg of nafarelin twice-daily (total 800 $\mu\text{g}/\text{day}$) by the intranasal route, starting in accordance with the center's normal practice. Down regulation was confirmed by no evidence of ovarian activity on ultrasound scan, endometrial thickness ≤ 10 mm, and estradiol ≤ 50 pg/mL or ≤ 180 pmol/L at least 10 days after commencement of the GnRH-a treatment. If down-regulation was not confirmed at that time, nafarelin treatment alone would be continued for up to 15 additional days. Down-regulation had to be confirmed before beginning treatment with r-FSH (Gonal-F®).

Recombinant FSH (Gonal-F®) was administered once-daily as a SC injection, in the abdomen at around the same time each day. The starting dose was in accordance with each center's normal practice and the history of the patient. The dose could be adapted according to the ovarian response monitored by ultrasound and plasma E₂ levels. The maximum cumulative dose allowed was 6 x 75 IU ampules (450 IU/day) and the maximum cumulative dose was not to exceed 100 x 75 IU ampules (7500 IU).

Nafarelin and Gonal-F® were administered until the criteria for induction of ovulation were met. hCG was administered within 24 hours of the last Gonal-F® and nafarelin injections.

When the follicular response was judged to be appropriate, (at least 1 follicle \geq 18mm diameter and at least 2 follicles \geq 16 mm and the estradiol level was approximately 150 pg/mL/follicle or 540 pmol/L/follicle) the patient was given (in a blinded fashion) 1 of the following 2 regimens:

- a SC injection of 250 μ g r-hCG (supplied in vials) and a SC injection of u-hCG placebo (supplied in ampules) or
- a SC injection of 5000 IU u-hCG (supplied in ampules) and a SC injection of r-hCG placebo (supplied in vials).

Human chorionic gonadotropin was withheld for failure of Gonal-F treatment (poor response), risk of OHSS, persisting cyst, non-compliance, adverse event, or discovery of ineligibility.

Micronized natural progesterone (600 mg/day) was administered by the vaginal route as luteal phase support, starting after the ovum pick-up (OPU). Progesterone treatment was continued until menstruation or for at least the first 3 weeks after diagnosis of pregnancy if the patient became pregnant.

11. Efficacy Assessments:

The primary efficacy endpoint in this study was the number of oocytes retrieved per patient who received hCG.

The number of oocytes retrieved was chosen as primary efficacy endpoint as it directly reflects the action of hCG on the follicles and is, therefore, adequate for assessment of efficacy. Furthermore, it has the advantage of allowing objective assessment and helps standardize results from different centers.

The secondary efficacy endpoints defined in the protocol comprised:

- Number of patients who received hCG with at least 1 oocyte retrieved
- Number of oocytes retrieved per number of follicles > 10 mm on the day of hCG
- Number of mature oocytes (i.e. metaphase I and II), when available
- Number of 2 PN fertilized oocytes
- Number of 2 PN cleaved embryos
- Serum P₄ level on day 1 post-hCG, on day of OPU, on day of ET and on DhCG6-7
- Serum hCG on the same days and at the same time points as P₄
- Implantation rate per embryo transferred
- Luteal phase endometrial thickness
- Number of biochemical and clinical pregnancies
- Number of multiple pregnancies
- Abortion rate (pregnancy loss per clinical pregnancy)
- Number of live births

12. Safety Assessments:

All adverse events occurring during the clinical study, as well as any serious adverse events, were to be reported in the appropriate section of the CRF. Information included type of adverse event, duration (onset/end dates), severity, relationship to study drug and any concomitant treatment dispensed or other action taken.

13. Disposition of Subjects:

A total of 235 subjects were screened for study entry. A total of 210 subjects were enrolled and received nafarelin treatment for down-regulation. A total of 205 subjects achieved down-regulation. A total of 190 patients received hCG, 186 subjects had 1 or more oocytes retrieved, and 166 subjects underwent embryo transfer.

14. Major Protocol Violations:

Of the 190 patients who received hCG, a total of 18 subjects, 9 in each treatment group, had major eligibility and protocol deviations and were non-evaluable. An additional five subjects had major deviations and did not receive hCG.

15. Demographic Characteristics:

Treatment groups were similar with respect to age, height, weight, smoking habits, past medical history, current medical conditions, medication prior to study drug administration, baseline physical examination including blood pressure and heart rate, type and duration of infertility, patients who had had a previous non-ART pregnancy or a previous miscarriage, ultrasound of the ovaries and uterus, hormonal screening, baseline semen analyses, duration and total dose of hCG, hormonal analyses during FSH treatment, and ultrasound assessments during FSH treatment.

There was a slight difference between the treatment groups in the number of subjects who had a previous ART attempt: 35 subjects treated with r-hCG had an average of 1.9 ART attempts while 39 subjects treated with u-hCG had an average of 1.5 attempts.

Of the subjects who received treatment, 97% were Caucasian.

16. Results.a. Efficacy:

Table 1

Efficacy Outcomes

Study 7648	Ovidrel® 250 mcg (n = 97)	Profasi® 5,000IU (n = 93)
Mean Number of oocytes retrieved per patient	10.6	10.6
Mean number of mature oocytes retrieved per patient	10.1	7.9
Mean number of 2 PN fertilized oocytes per patient	5.7	5.4
Mean number of 2 PN or cleaved embryos per patient	5.1	4.3
Implantation rate per embryo transferred (%)	17.4	14.1
Mean mid-luteal serum progesterone levels (nmol/L)	394	330
Clinical pregnancy rate per initiated treatment cycle (%)	33	24.7
Clinical pregnancy rate per transfer (%)	37.6	28.4

The primary efficacy endpoint was the number of oocytes retrieved per subject at ovum pickup following injection with hCG. The mean number of oocytes retrieved was similar across the two treatment groups. The limits of the 2-sided 90% confidence interval fell within the acceptable clinically relevant range

of 3 oocytes. The mean number of mature oocytes was lower in the Profasi group than in the r-hCG group and this difference approached statistical significance ($p=0.067$). The mean number of 2 PN cleaved embryos was higher in the r-hCG group, but not statistically significantly different. The serum progesterone levels were similar between the treatment groups at ovum pickup and embryo transfer, but at the mid-luteal phase assessment, the serum progesterone levels were higher in the r-hCG group with the difference approaching statistical significance ($p=0.066$). The mean implantation rate per embryo-transferred was higher in the r-hCG group, but not statistically significantly different. The proportion of subjects achieving clinical pregnancy was similar between the treatment groups.

All confirmed clinical pregnancies were followed until the time of pregnancy completion, delivery, or pregnancy loss.

Anencephaly was detected in the fetus of one subject who received Ovidrel.

Table 2
Pregnancy Outcomes by Treatment Group

Pregnancy Outcome	Ovidrel n = 97	Profasi n = 93
Clinical Pregnancies	32	23
Ectopic Pregnancies	1 (3.1%)	1 (4.3%)
Spontaneous Abortions	4 (12.5%)	0
Other	1 (3.1%)	1 (4.3%)
Live Births	26 (81.2%)	21 (91.3%)
Singletons	18 (69.2%)	13 (61.9%)
Twins	8 (30.8%)	8 (38.1%)

There was no significant difference in the proportion of subjects having a live birth, ectopic pregnancy, or spontaneous abortion.

b. **Safety:**

Table 3

Adverse Events after hCG Administration

Adverse Event	Ovidrel n = 97		Profasi n = 93	
		%		%
Inflammatory Swelling	1	1.0	1	1.1
Injection Site Bruising	7	7.2	7	7.5
Injection Site Inflammation	3	3.1	19	20.4
Injection Site Pain	7	7.2	22	23.7
injection Site Reaction	1	1.0	1	1.1
Dizziness			2	2.2
Abdominal Pain	2	2.1		
Appendicitis			1	1.1
Bloating			1	1.1
Abdominal Colic	1	1.0		
Diarrhea			1	1.1
Nausea			1	1.1
Vomiting	1	1.0		
Increased Hepatic Enzymes			1	1.1
Cervical Carcinoma	1	1.0		
Ovarian Hyperstimulation	1	1.0	1	1.1
Vaginal Hemorrhage	1	1.0		
Abscess	1	1.0		
Vaginal Mycosis	1	1.0		
Bronchitis			1	1.1
Rhinitis	1	1.0	1	1.1
Itching			1	1.1
Urinary Tract Infection	2	2.1		

Seven of the adverse events occurring after hCG administration (2 with Ovidrel and 5 with Profasi) were severe or life threatening.

Subject 3-16 menstruated 12 days after receiving Ovidrel. She experienced continuous abdominal pain and required hospitalization for about a week. A diagnosis of pancreatitis was made. This event was unrelated to Ovidrel.

Subject 7-02 received Ovidrel, but had no oocytes retrieved on the day of ovum pick-up. Irregular vaginal bleeding began and a month later

the subject was diagnosed as having carcinoma of the cervix. Her most recent Pap smear, taken 3 years before, was negative. This event, while life threatening, was unrelated to Ovidrel.

Three subjects receiving Profasi experienced severe injection site pain and one subject receiving Profasi experienced severe ovarian hyperstimulation syndrome which were related to Profasi. One subject receiving Profasi developed appendicitis eight days after the Profasi injection. This event was unrelated to the Profasi.

There were 7 serious events in 6 subjects which occurred during pregnancy or at the time of delivery (3 with Ovidrel and 4 with Profasi).

After Ovidrel treatment and subsequent pregnancy, subject 4-03 had an emergency Cesarean section because of fetal bradycardia and delivered a 3.3 kg baby. The baby died 6 days later. This event was unrelated to Ovidrel.

Subject 6-40, an Ovidrel-treated subject, had an ultrasound scan at 16 weeks of pregnancy which showed a severe acrania. The subject had an abortion. Autopsy confirmed the diagnosis. The relation between this event and Ovidrel was unknown to the investigator.

Subject 7-34 had a complete abortion of twins at 10 weeks gestation after receiving Ovidrel. This event was unrelated or remotely related to Ovidrel.

Subject 5-05 had an ectopic pregnancy after receiving Profasi. The relationship to Profasi was unknown to the investigator.

Subject 5-10, a Profasi-treated subject, experienced a vaginal β -hemolytic streptococcal infection which induced premature labor. Twins weighing 1.480 kg and 1.470 kg were delivered. One baby died as a result of the infection. This event was unrelated or remotely related to Profasi.

Subject 7-19, a Profasi-treated subject, had an ultrasound scan at 19 weeks of gestation. Two congenital anomalies were detected. The fetus was noted to have a shortened right arm with an absent radius and clubbing of the right hand. The fetus was also noted to have a cardiac defect with pulmonary artery stenosis and right ventricular hyperplasia. The baby was karyotypically normal and the subject elected to continue with the pregnancy. A boy weighing 2.140 kg was delivered. This event was unrelated or remotely related to Profasi.

Overall, hCG injections were well tolerated. However, a significantly higher proportion of subjects reported local inflammation and pain after Profasi injections than after Ovidrel injections.

No difference was noted in hematology and biochemistry values between Ovidrel and Profasi recipients.

A total of 152 subjects had samples assayed for anti-hCG antibodies. All were found to be negative.

B. Study 7927:

"A phase III, open, comparative, randomized, multicenter study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin (r-hCG), administered subcutaneously, with that of urinary human Chorionic Gonadotropin (Profasi®), intramuscularly, for inducing final follicular maturation and early luteinization in women undergoing superovulation with highly-purified human Follicle Stimulating Hormone (Fertinex™ (Metrodin XP™) prior to IVF/ET".

1. Investigators:

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2. Objectives of the Study:

The objectives of this study were to assess the safety and the efficacy of r-hCG administered SC compared with Profasi® administered IM for inducing final oocyte maturation and initiation of follicular luteinization in patients who have undergone pituitary desensitization and superovulation as part of an IVF/ET cycle.

3. Rationale for the Study:

In vitro fertilization (IVF) of human oocytes followed by the replacement of the embryo in the uterine cavity (embryo transfer, ET) is a well established treatment for female infertility attributable to damaged fallopian tubes, endometriosis or unexplained causes.

In IVF/ET, the pregnancy rate is proportional to the number of embryos replaced in the uterus. This has its limitations in practice, given that multiple embryo transfer carries the risks associated with multiple pregnancy. Therefore, it is recommended to replace not more than three embryos during any one procedure.

Normally, a single follicle develops during the menstrual cycle leading to the maturation and ovulation of one oocyte. In IVF, in order to optimize the chance of pregnancy, it is necessary to obtain more than one embryo by stimulating the growth and maturation of several follicles. Such multiple follicular development is obtained by daily administration of human Follicle Stimulating Hormone (hFSH). When these follicles have reached a diameter ≥ 18 mm, human Chorionic Gonadotropin (hCG) is injected to achieve final oocyte maturation and initiation of follicular luteinization.

A more recent improvement in stimulation protocols for IVF has been the addition of long-acting agonists of Gonadotropin Releasing Hormone (GnRH) to the gonadotropin treatment regimen. The purpose of employing these agonists is to provide a more homogenous cohort of follicles and prevent premature luteinization of the follicles through prevention of premature endogenous LH surge.

Recombinant human chorionic gonadotropin is being developed as a pharmaceutical product to replace urinary human chorionic gonadotropin. The advantage of recombinant hCG are high purity and specific activity, batch-to-batch consistency, and independence from urine collection.

4. Method of Assignment to Treatment:

Subjects were randomly assigned to treatment groups in blocks of 6 subjects after meeting the criteria for the administration of human chorionic gonadotropin.

5. Number of Subjects:

A total of 296 subjects achieved down-regulation and received at least one injection of hFSH. Of these, 275 subjects were randomized to 250 μg r-hCG (94 subjects), 500 μg r-hCG (89 subjects), or to 10,000 U Profasi (92 subjects).

6. Duration of Clinical Trial:

One treatment cycle only (a single injection)

7. Inclusion Criteria:

- a. Infertile woman. Defined as a woman desiring a pregnancy and having failed to conceive after at least two years of unprotected coitus, except where bilateral tubal obstruction was documented. The couple's infertility could have been attributable to any of the following: tubal factor, mild endometriosis (American Fertility Society classification stage I or II) or unexplained. In the case of unexplained infertility, the history had to be at least 3 years, and a post-coital test had to show at least one forward progressive sperm per high-powered field.
- b. A male partner with semen analysis within the past 6 months within acceptable values. Donor sperm was acceptable if it met the criteria.
- c. Aged 18 to 38 years (before 39th birthday)
- d. Negative pregnancy test prior to beginning Lupron® therapy
- e. Regular spontaneous ovulatory menstrual cycles of 25 to 35 days
- f. During early follicular phase (Day 2-4, inclusive), serum levels of the following hormones assayed in the central laboratory within the ranges defined below:

- FSH not above the upper limit of normal for the early

follicular phase.

- LH not above the upper limit of normal for the early follicular phase
- Prolactin, Testosterone and TSH within the normal range.
- E2 <75 pg/mL

- g. No clinically significant abnormal hematology, chemistry or urinalysis according to central laboratory criteria
- h. Presence of both ovaries
- i. No more than one previous assisted conception cycle (GIFT, ZIFT, ICSI, SUZI, or IVF) in which gonadotropin stimulation was employed.
- j. No treatment with clomiphene citrate or gonadotropins for at least 2 months prior to treatment in this study.
- k. No assisted conception treatment for at least 2 full menstrual cycles.
- l. HIV negative
- m. Hepatitis B surface antigen negative
- n. Willingness to participate and comply with the protocol for the duration of the study.
- o. Signed informed consent form

8. Exclusion Criteria:

- a. Clinically significant systemic disease (e.g., insulin - dependent diabetes, epilepsy, severe migraine, intermittent porphyria, hepatic, renal or cardiovascular disease, severe corticosteroid-dependent asthma).
- b. Any contraindication to being pregnant and/or carrying a pregnancy to term.
- c. Extrauterine pregnancy in the past 3 months
- d. A body mass index greater than 30 kg/m²

- e. Polycystic ovarian syndrome (PCOS), defined on study screening ultrasound as an ovary containing in one section ≥ 10 follicles measuring between 3 and 10 mm in diameter (day 2-4, inclusive)
- f. Previous history of severe OHSS
- g. Any medical condition which in the judgment of the investigator and sponsor may have interfered with the absorption, distribution, metabolism or excretion of the drug.
- h. Previous IVF or GIFT failure due to a problem of either sperm fertilization ($\leq 20\%$ of all eggs retrieved), or a poor response to gonadotropin therapy. Poor responders were defined as women who matured ≤ 2 follicles in a previous attempt or who required $\geq 6,000$ IU of FSH/hMG in the treatment cycle
- i. Abnormal gynecological bleeding of undetermined origin
- j. No more than three prior pregnancy losses
- k. Previous history of intolerance to hMG, FSH, GnRH agonists or to hCG
- l. Simultaneous participation in another clinical trial
- m. Known active substance abuse (including smokers consuming more than 10 cigarettes/day).
- n. Refusal or inability to comply with the protocol
- o. Abnormal uterine cavity

9. Trial Period:

February 1996 - April 1998

10. Dosage and Mode of Administration:

Once patients met all of the eligibility criteria and had been included in the trial, down-regulation was to be achieved by the daily administration of 1.0 mg Lupron® by SC injection into the thigh or arm starting 7 to 8 days post-ovulation. Once down-regulation had been documented (estradiol <75 pg/mL), the

dose of Lupron® was to be decreased to 0.5 mg daily and continued up to and including the day of hCG administration. Treatment with hFSH (Fertinex™) was to begin following the establishment of down-regulation at a dose of 225 IU/day for the first five treatment days. At the discretion of the investigator, the dose could have been increased by 75 to 150 IU/day, every 2 to 3 days, if the patient's response was judged to be slow. Dosing with hFSH was to continue until follicular development was judged to be adequate. Human chorionic gonadotropin was withheld in subjects with inadequate follicular response, risk of OHSS, protocol violation, or patient's decision. Based on randomization, patients were to receive a single dose of r-hCG SC at a dose of 250 or 500 µg or Profasi® IM at a dose of 10,000 USP units 36 hours after the last hFSH injection. Progesterone in Oil was to be administered IM daily at a dose of 50 mg beginning within 24 hours of OPU for luteal phase support.

11. Efficacy Assessments:

The primary efficacy endpoint in this study was the number of oocytes retrieved per subject who received hCG. The secondary efficacy endpoints were:

- Number of patients with at least one oocyte retrieved who received hCG
- Number of oocytes retrieved per number of follicles on the day of hCG (pre-hCG)
- Number of mature oocytes (i.e. metaphase I+metaphase II), when available
- Number of 2 PN fertilized oocytes
- Number of 2 PN or cleaved embryos
- Implantation rate per embryo transferred
- Serum progesterone and serum hCG level on day of OPU, on day of ET and on day 6 or 7 post hCG
- Luteal phase endometrial thickness
- Number of pregnancies:

- Number of biochemical pregnancies
- Number of clinical pregnancies (fetal sac with or without fetal heart activity on ultrasound)
- Number of multiple pregnancies (percentage of twins and triplets)
- Abortion rate (pregnancy loss per clinical pregnancy)
- Number of live births

12. Safety Assessments:

- a. Incidence and severity of adverse events
- b. Local tolerance at injection sites
- c. Anti-hCG and anti-FSH antibodies
- d. Pathological changes in clinical laboratory parameters
- e. Pregnancy outcome

13. Disposition of Subjects:

A total of 389 subjects were screened for study entry. A total of 297 subjects were enrolled and received treatment with Lupron for down-regulation. A total of 296 subjects were treated with FSH and 275 subjects were randomized, received a single dose of hCG, and had 1 or more oocytes retrieved. Embryo transfer was completed in 263 subjects.

14. Major Protocol Violations:

Violations of the protocol were generally minor and did not affect the outcome of the study. None of the 275 randomized subjects who received a dose of hCG were excluded from efficacy analyses. All subjects had data available and were included.

15. Demographic Characteristics:

The three hCG treatment groups were not different with regard to all demographic characteristics assessed. The median age of the 275 hCG-treated patients was 32 years at the time of hFSH dose, with a range of 24 to 38 years; the majority of the patients were Caucasian (80.7%) and were non-smokers (91.3%). Median weight among the 275 patients was

135 lbs; median BMI was 23 kg/m². Demographic characteristics for the 21 non-randomized patients was similar to that observed for those patients who were randomized.

16. **Results:**

a. **Efficacy:**

Table 4

Characteristics of Non-randomized and Randomized Subjects Just Prior to Randomization

Study 7927	Non-randomized	Randomized
	(n=21)	(n=275)
Mean # of follicles >10mm	6.4	13.8
Mean # of follicles ≥ 16mm	1.9	7.2
Mean # of follicles ≥ 18mm	0.9	3.9
Serum Estradiol (pmol/L)	3016	6523

**APPEARS THIS WAY
ON ORIGINAL**

Table 5

Treatment Outcomes by Treatment Group

Study 7927	Ovidrel® 250mcg (n = 94)	Ovidrel® 500 mcg (n = 89)	Profasi ® 10,000 USP Units (n = 92)
Mean number of oocytes retrieved per patient	13.60	14.64	13.66
Mean number of mature oocytes retrieved per patient	7.6	9.4	9.7
Mean number of 2 PN fertilized oocytes per patient	7.2	8.8	7.8
Mean number of 2 PN or cleaved embryos per patient	7.6	9.7	8.2
Implantation rate per embryo transferred (%)	18.7	21.3	17.3
Mean mid-luteal serum progesterone levels (nmol/L)	423	520	469
Clinical pregnancy rate per initiated treatment cycle (%)	35.1	36	35.9
Clinical pregnancy rate per transfer (%)	36.3	38.6	37.1

The primary efficacy endpoint in this study was the number of oocytes retrieved per patient at OPU conducted 34 to 38 hours following injection with hCG. Statistical analysis was performed by constructing a 90% confidence interval (CI) on the difference between two pairs of treatment groups (500 μ g r-hCG and Profasi®; 500 μ g r-hCG and 250 μ g r-hCG). Each treatment pair was to be declared equivalent if the limits of the confidence interval fell within the acceptable relevant range of ± 3 oocytes. The mean number of oocytes retrieved per patient 13.60, 14.64, and 13.66 for the 250 μ g r-hCG group, the 500 μ g r-hCG group and the

Profasi® group, respectively. The mean difference between the 500 µg r-hCG group and the Profasi® group was 0.98 with a 90% CI of (-0.775, 2.729). For the comparison of the 500 µg and the 250 µg r-hCG groups, the mean difference was 1.04 with a 90% CI of (-0.706, 2.781). For treatment equivalence to be declared the lower bound of the 90% CI for the differences between number of oocytes retrieved had to be greater than -3 oocytes and the upper bound had to be less than 3 oocytes. Thus, the 500 µg dose of r-hCG group is equivalent in treatment efficacy to Profasi® and, likewise, the 250 µg and 500 µg doses are equivalent in efficacy, by this parameter.

No statistically significant differences were observed between the 500 µg r-hCG and the Profasi® group for the secondary endpoints, number of mature oocytes retrieved and implantation rate. However, differences of some clinical importance were observed between the 500 µg and 250 µg r-hCG groups for a number of secondary efficacy endpoints. Patients in the 500 µg r-hCG treatment group had a statistically significantly higher number of 2 PN fertilized oocytes as compared to the 250 µg r-hCG group. There was no corresponding difference between the 500 µg r-hCG group and the Profasi® group for this parameter. A difference was also observed for the number of 2 PN or cleaved embryos between the r-hCG 500 µg and r-hCG 250 µg dose groups. Again, there was no corresponding difference between the 500 µg r-hCG and the Profasi® treatment groups. Mid-luteal phase serum progesterone levels were also significantly higher in the 500 µg r-hCG as compared to the 250 µg r-hCG group, while the difference between the 500 µg r-hCG and Profasi® groups was not statistically significant. Although these clinically important differences were noted, there were however, no differences observed in clinical pregnancy rates or pregnancy outcome between the two r-hCG dose groups. The sponsor states that this absence of difference in pregnancy data may be explained by the limitation in number of embryos that may be replaced in a treatment cycle, thus correcting back any differences achieved in earlier assessments of outcome. Overall, therefore, the impact of clinically significant differences in secondary efficacy endpoints may be masked within the limited number of embryos that may be replaced in an ART study. On the other hand, since there were equivalent numbers of oocytes retrieved, one would expect an equivalent number of good quality oocytes for fertilization, and an equivalent number of good quality embryos resulting in equivalent numbers of pregnancies.

A total of 98 (35.6%) of the 275 randomized patients had a clinical pregnancy including 33 (35.1%) of 94 patients in the 250 µg r-hCG group, 32 (36.0%) of 89 patients in the 500 µg r-hCG and 33 (35.9%) of 92 patients in the Profasi® group. There were no statistically significant

differences in patient clinical pregnancy rate for either treatment pair comparison. The outcomes of the pregnancies are presented by treatment group in Table 6.

Table 6

Pregnancy Outcomes by Treatment Group

Study 7927	Ovidrel® 250 mcg (n = 33)	Ovidrel® 500mcg (n = 32)	Profasi® 10,000 USP Units (n = 33)
Pregnancies (Clinical) not reaching term	4 of 33 (12.1%)	5 of 32 (15.6%)	5 of 33 (15.2%)
Live Births	29 of 33 (87.9%)	27 of 32 (84.4%)	28 of 33 (84.8%)
Single Births	20 of 29 (69.0%)	17 of 27 (63.0%)	14 of 28 (50.0%)
Multiple Births	9 of 29 (31.0%)	10 of 27 (37.0%)	14 of 28 (50.0%)

The study findings are comparable to those reported in the medical literature for IVF/ET treatment of infertile women.

One 37 year old subject who received Ovidrel 500 mcg delivered triplets, one of whom was diagnosed with Down's syndrome and atrial septal defect.

b. Safety:

Adverse events reported in at least 2% of subjects, regardless of causality, are listed in Table 7 by treatment group for the Ovidrel 250 μ g and 500 μ g treatment arms. The incidence of adverse events occurring in the Profasi treatment arm was very similar to those occurring in the Ovidrel 250 μ g group. The most common adverse events reported were post-operative pain, nausea, abdominal pain, and ovarian hyperstimulation. These events occurred at a higher rate in the Ovidrel 500 μ g arm than in the other two treatment arms. Ovarian hyperstimulation syndrome was reported in 3 subjects (3.2%) in the Ovidrel 250 μ g group, in 3 subjects (3.1%) in the Profasi group, and in 8

subjects (9.0%) in the Ovidrel 500 μg group. Ovarian hyperstimulation syndrome, as a serious adverse event, occurred more often in the Ovidrel 500 μg group (3 of 89 subjects) than in the Ovidrel 250 μg group (1 of 95 subjects) and the Profasi group (0 of 96 subjects). Two of the subjects with OHSS reported as serious adverse events, both in the Ovidrel 500 μg group, had severe OHSS and discontinued the study due to the event. The other two subjects with OHSS reported as serious adverse events had moderate OHSS.

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Table 7

Adverse Events After hCG Administration

Adverse Event	250 mcg Ovidrel® n = 95 (%)	500 mcg Ovidrel® n = 89 (%)
Nausea	8 (8.4%)	13 (14.6%)
Abdominal Pain	8 (8.4%)	10 (11.2%)
Vomiting	5 (5.3%)	7 (7.9%)
Flatulence	2 (2.1%)	0
Diarrhea	2 (2.1%)	0
Ovarian Hyperstimulation	3 (3.2%)	8 (9.0%)
Intermenstrual Bleeding	2 (2.1%)	4 (4.5%)
Pregnancy, Ectopic	1 (1.1%)	2 (2.2%)
Post-Operative Pain	11 (11.6%)	14 (15.7%)
Pain	4 (4.2%)	2 (2.2%)
Fever	2 (2.1%)	0
Fatigue	0	2 (2.2%)
Headache	3 (3.2%)	3 (3.4%)
Dizziness	2 (2.1%)	2 (2.2%)
Injection Site Pain	2 (2.1%)	3 (3.4%)
Injection Site Reaction	2 (2.1%)	2 (2.2%)
Rash	3 (3.2%)	1 (1.1%)
Insomnia	2 (2.1%)	0
Upper Respiratory Tract Infection	2 (2.1%)	1 (1.1%)
Dysuria	2 (2.1%)	1 (1.1%)

Additional adverse events not listed in Table 7 that occurred in less than 2% of patients treated with Ovidrel® included: hiccup, vaginal hemorrhage, cervix lesion, dysmenorrhea, leukorrhea, ovarian disorder,

uterine hemorrhage, vaginitis, uterine disorder, vaginal discomfort, back pain, syncope, hot flashes, malaise, flu-like symptoms, paraesthesias, application site disorders occurring including bruising, inflammation, and swelling at the injection site, sweating, emotional lability, confusion, depression, cough, dyspnea, urinary incontinence, albuminuria, cardiac arrhythmia, tachycardia, genital moniliasis, genital herpes, leukocytosis, leucopenia, goiter, heart murmur, anemia and fibroadenosis of the breast.

Twelve of the 296 subjects who received at least one dose of hFSH experienced serious adverse events.

Two of the 12 received Profasi and both had ectopic pregnancies.

The other 10 subjects received Ovidrel. Three of them had ectopic pregnancies, 4 of them had ovarian hyperstimulation (2 severe OHSS and 2 moderate OHSS), and 1 each had ovarian torsion, vasovagal reaction, and abdominal pain.

Patients were asked to record on a diary card any injection site reactions they experienced after injection with hCG. Five categories of symptoms were recorded: itching, redness, swelling, bruising and pain.

The three treatment groups were similar with regards to injection site reactions. Within each symptom category (itching, redness, swelling, bruising, or pain), 95% or more of the injections assessed had no reaction or only a mild reaction reported. Maximum severity reported was assessed as no reaction or only a mild to moderate reaction for itching, redness and swelling. Severe bruising was reported in one patient in the 250 μ g r-hCG group and severe pain was reported in five patients including three in the 250 μ g r-hCG group and two in the 500 μ g r-hCG group.

No differences in shifts were observed between the treatment groups for either clinical chemistry or hematology. The majority of patients in both groups had laboratory values in the normal range at both the baseline and endpoint (end-of-study) assessments. Approximately 8.8% of subjects did exhibit a rise in ALT from pre-to post-study. Results were similar across the three hCG treatment groups. The median change from baseline was from 14.0 to 16.5 and the mean change from baseline was from 15.7 to 20.4. The mean increase in ALT was 2.19 in the Ovidrel 250 μ g group, 5.14 in the Ovidrel 500 μ g group, and 6.70 in the Profasi group. Six subjects in the Ovidrel 250 μ g group did have a rise in ALT from normal to high. The most dramatic rise was from 13.0 to 43.0. The most dramatic rise in the Ovidrel 500 μ g group and the Profasi group were from 16.0 to 93.0 and from 16.0 to 150.0 respectively. Bilirubin remained

unchanged in all groups. The mean change in alkaline phosphatase was from 61.4 to 63.5.

Two subjects receiving Ovidrel and one subject receiving Profasi had post-study elevated white blood cell counts. These three subjects had ovarian hyperstimulation and the elevated white blood cell counts were consistent with this diagnosis.

Two-hundred seventy-eight (278) of the 296 patients had samples available for determination of serum antibodies to FSH and hCG prior to initiation of the study and in 270 patients post-study samples were available.

Retrospective hCG antibody testing revealed one positive result. At the baseline visit, Patient 130006, a 35 year-old gravid 2, para 0, with secondary infertility, had a positive anti-hCG titer (ratio 2.3). This was an unexpected finding as the patient had no prior history of treatment with fertility drugs, including hCG. In accordance with the study protocol, she was treated with FSH from 1/10/97-1/20/97 and received 500 mcg r-hCG on 1/21/97. At the post-study visit on 2/6/97, the hCG antibody result was negative.

C. Study 8209:

"A phase III, double-blind, double-dummy, randomized, multicenter study to compare the safety and efficacy of recombinant human Chorionic Gonadotropin (Ovidrel®) with that of urinary human Chorionic Gonadotropin (Profasi®) in inducing ovulation in anovulatory infertile women undergoing stimulation of follicular development with recombinant human Follicle Stimulating Hormone (Gonal-F®)".

1. Investigators and Country:

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2. Objectives of the Study:

The objectives of this study were to assess the safety and efficacy of r-hCG (Ovidrel®) compared with u-hCG (Profasi®), both administered SC, in inducing ovulation in patients who have undergone stimulation of follicular growth with r-FSH (Gonal-F®), and to document the safety of SC administration of r-hCG and to compare it with SC administration of u-hCG. The primary objective was to show clinical non-inferiority of r-hCG compared with u-hCG in terms of number of patients who achieved ovulation in each group.

3. Rationale for the Study:

Recombinant human chorionic gonadotropin is being developed as a pharmaceutical product to replace urinary human chorionic gonadotropin. Producing hCG through recombinant DNA technology provides high purity and specific activity, batch-to-batch consistency, and independence from urine collection.

4. Method of Assignment to Treatment:

On the day of hCG administration, the subject was allocated in sequential order the next lowest available randomization number, and was administered the assigned hCG medication in a blinded fashion.

5. Number of Subjects:

A total of 198 subjects were randomized and received hCG. Of these, 177 were evaluable and analyzed as the per protocol data set. The all subjects data set was also analyzed.

6. Duration of Clinical Trial:

One cycle of induction of ovulation (a single injection of hCG)

7. Inclusion Criteria:

- a. Be a woman between her 20th and 39th birthday
- b. Be infertile due to ovulatory dysfunction and wishing to conceive
- c. Be anovulatory or oligo-ovulatory
- d. Have spontaneous menses, menses induced by clomiphene citrate therapy or a positive progestogen-induced withdrawal bleed within the previous year.
- e. Have not received more than 10 cycles of clomiphene citrate or gonadotrophins
- f. Have normal hormonal values in a blood sample, drawn within 3 months before treatment start
- g. No clinically significant abnormal findings, within 6 months before treatment start, among pre-treatment hematology, chemistry and urinalysis parameters or results of no pathological significance if outside normal limits
- h. Two patent tubes as documented by recent (within 3 years prior to treatment assignment) hysterosalpingography (HSG) or laparoscopy
- i. No pelvic inflammatory disease (PID) between the previous assessment and study entry
- j. Normal uterine cavity as documented by recent (within 5 years prior to treatment assignment) hysteroscopy, HSG or ultrasound scan
- k. Male partner with semen analysis within the values defined

and no significant infection within the past 6 months

- i. No treatment with clomiphene citrate or gonadotrophins for at least 2 months prior to pre-study evaluation
- m. Negative pregnancy test prior to beginning stimulation therapy
- n. A body mass index ≥ 18 and ≤ 35 kg/m²
- o. Able to communicate well with the Investigator and to comply with the requirements of the entire study
- p. Have given written informed consent prior to any invasive pre-study screening procedure, with the understanding that consent may be withdrawn by the patient at any time without prejudice

8. Exclusion Criteria:

- a. Any medical condition which in the judgement of the Investigator may interfere with the absorption, distribution, metabolism or excretion of the drug. In case of doubt the patient in question was discussed with Ares-Sefono's Therapeutic Director
- b. Any contraindication to being pregnant and/or carrying a pregnancy to term
- c. Clinically significant systemic disease (e.g. insulin-dependent diabetes, epilepsy, severe migraine, intermittent porphyria, hepatic, renal or cardiovascular disease, severe corticosteroid-dependent asthma)
- d. Anovulation due to anorexia or strenuous physical exercise (e.g. for competition purposes)
- e. Persistent ovarian cyst with a diameter > 20 mm or ovarian endometrioma on ultrasound
- f. Myomatous uterus which in the opinion of the Investigator could impair pregnancy evolution
- g. Known severe endometriosis (American Fertility Society classification III or IV)

- h. Abnormal bleeding from the reproductive tract of undetermined origin
- i. Previous history of severe ovarian hyperstimulation syndrome
- j. Previous history of intolerance of FSH or of hCG
- k. Known to be HIV positive
- l. Hepatitis B surface antigen positive (unless vaccinated) or known to be Hepatitis B or C positive
- m. Simultaneous participation in another clinical trial
- n. Active substance abuse (e.g. smokers consuming more than 20 cigarettes/day)
- o. Refusal or inability to comply with the protocol

9. Clinical Trial Period:

March 1996 - May 1999

10. Dosage and Mode of Administration:

Gonal-F, at a dose of 75 IU/day, was administered for 14 days with dose adjustments permitted after 14 days as required. Ovarian response was monitored by ultrasound examination of the ovaries and serum estradiol assessments.

hCG was administered within 24 hours of the last r-hFSH injection. When the follicular response was judged to be appropriate, (1 follicle \geq 18mm, E_2 no higher than 5500 pmol/L) the patient was given (in a blinded fashion) 1 of the following 2 regimens:

- A SC injection of 250 μ g r-hCG (supplied in vials) and a SC injection of u-hCG placebo (supplied in ampules) or
- A SC injection of 5000 IU u-hCG (supplied in ampules) and a SC injection of r-hCG placebo (supplied in vials).

11. Efficacy Assessments:

Human chorionic gonadotropin was withheld if there was lack of response to r-hFSH, risk of OHSS, pregnancy, or serious adverse event. No luteal support was given after hCG. Either timed intercourse or intra-uterine insemination was used for insemination.

The primary variable in this study was ovulation. Ovulation was defined as a mid luteal phase serum $P_4 \geq 30$ nmol/L (9.4 ng/mL). The higher of the 2 values obtained from 2 samples in the central laboratory was to be taken into account for efficacy analysis of this study in all patients receiving hCG and having $P_4 < 30$ nmol/L before hCG injection. If a clinical pregnancy was obtained, whether or not mid-luteal phase P_4 was ≥ 30 nmol/L, the cycle was to be considered as a success.

The secondary efficacy variables defined in the protocol comprised:

- Mean luteal serum P_4 levels of the 2 assessments between days 5-10 post-hCG
- Visualization of the ovulation by ultrasound, in the centers currently using this method
- Serum hCG on days 0 and on days 1 and 2 post-hCG and on the same days and same time points as P_4 for pharmacokinetics/pharmacodynamics analysis, as well as serum hormonal levels (e.g. androstenedione, E_2)
- Luteal phase endometrial thickness
- Number of biochemical and clinical pregnancies
- Number of multiple pregnancies
- Abortion rate (pregnancy loss per clinical pregnancy)
- Number of live births
- Luteal phase duration for non-pregnant patients

12. Safety Assessments:

Incidence and severity of adverse events, including the incidence and severity of ovarian hyperstimulation syndrome, clinically significant changes in routine laboratory tests, local tolerance of r-hCG and u-hCG, development of antibodies to hCG, and changes in vital signs were to be recorded and evaluated.

13. Disposition of Subjects:

A total of 329 subjects were screened for study entry, of which 242 subjects were enrolled. All 198 subjects who achieved successful stimulation were randomized to one of the two hCG treatments. A total of 99 subjects received r-hCG and 99 received u-hCG. A total of 177 subjects were found to be evaluable and were analyzed as the per protocol data set. The all subjects data set was also analyzed.

14. Major Protocol Violations:

Three subjects with major eligibility criteria deviations plus 18 subjects with major deviations from the study were excluded from the per protocol data set analyses.

15. Demographic Characteristics:

Of the 198 subjects who received treatment, 183 were Caucasian, 8 were Asian, 6 were Black, and 1 was of mixed race. Treatment groups were similar with respect to age, height, weight, smoking habits, current medical conditions unrelated to the study condition, concomitant medication prior to study drug administration, baseline physical examination, type of infertility, duration of infertility, ovarian characteristics, uterine characteristics, and results of hormonal screening.

16. Results:

a. Efficacy:

Almost all subjects ovulated, defined as midluteal $P_4 > 9.4$ ng/mL (30 nmol/L). In the per protocol analysis, 95.3% of subjects receiving r-hCG and 88.0% of subjects receiving u-hCG ovulated. In the all subjects analysis, 91.9% of subjects receiving r-hCG and 85.9% of subjects receiving u-hCG ovulated. The estimate of the effect of taking r-hCG

rather than u-hCG is +6.0% and the lower limit of the 1-sided 95% CI for the treatment effect is -3.7%. As this is above the clinically acceptable limit of -20% as pre-defined in the protocol, it can be concluded that r-hCG is not statistically inferior to u-hCG. The secondary efficacy variables confirmed the results of the primary variable. No statistically significant differences were found between the treatment groups for the majority of secondary variables. A total of 51 subjects were clinically pregnant (22 r-hCG, 29 u-hCG) and 45 subjects had continuing pregnancies.

Table 8

Mean Progesterone (nmol/L) - All Subjects Analysis

Study 8209	r-hCG	u-hCG
DhCG 2-3	21.9	17.2
DhCG 5-7	78.4	55.8
DhCG 8-10	59.9	52.6

Table 9

Clinical Pregnancy Outcomes by Treatment Group

Clinical Pregnancy Outcomes Study 8209	Ovidrel n = 22	Profasi n = 29
Clinical Pregnancies not reaching term	7 of 22 (31.8%)	5 of 29 (17.2%)
Live Births	14 of 22 (63.6%)	20 of 29 (69.0%)
Single Births	12 of 14 (85.7%)	17 of 20 (85.0%)
Multiple Births	2 of 14 (14.3%)	3 of 20 (15.0%)
Ongoing Pregnancies	1 of 22 (4.5%)	4 of 29 (13.8%)

A 38 year old subject receiving Ovidrel had an amniocentesis performed because of her age and a fetal chromosomal abnormality (47,XXX) was diagnosed. Both patient and her husband had normal chromosomal Karyotype.

b. Safety:

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Table 10

Adverse Events After hCG Administration

Adverse Event	r-hCG (n = 99) % of patients	u-hCG (n = 99) % of patients
Injection site bruising	3.0	7.1
Injection site inflammation	2.0	15.2
Injection site pain	8.1	17.2
Injection site reaction	3.0	7.1
Abdominal Distension	1.0	
Influenza-like Symptoms		1.0
Abdominal Discomfort	1.0	
Abdominal Pain	2.0	3.0
Abdominal Pain, Lower		3.0
Bloating	1.0	
Hyperglycemia	1.0	
Breast Abscess		1.0
Breast Pain, Female	1.0	1.0
Ovarian Cyst	3.0	4.0
Ovarian Hyperstimulation	3.0	
Infection, Fungal		1.0
Throat, Sore	1.0	
Upper Respiratory Tract Infection	1.0	
Itching	1.0	
Hematuria		1.0
Leukocytosis		1.0

A significantly higher proportion of subjects reported at least one injection site symptom after Profasi than after Ovidrel injections; 31 injections out of 99 u-hCG injections (31%) led to at least one report, while 9 out of 99 injections of r-hCG (9.1%) led to such reports. Also, r-hCG does not appear to result in more local reactions than placebo, contrasting with u-hCG which did. (Each subject received two subcutaneous injections, one hCG and one placebo.)

Three subjects receiving Ovidrel had symptoms of OHSS lasting 3, 5, and 19 days, respectively. One subject had clinically significant ascites and became pregnant. None of the subjects required hospitalization.

Overall, assessment of hematology, chemistry, and urinalysis before and after therapy did not show any clinically relevant differences between the treatment groups.

A total of 177 subjects who received hCG had samples assayed for anti-hCG antibodies. All were found to be negative.

IX. Reviewer's Overall Comments and Evaluation of Clinical Studies:

Studies 7648 and 7927 assessed the efficacy and safety of Ovidrel compared with Profasi for inducing final oocyte maturation and initiation of follicular luteinization and superovulation as part of an IVF/ET cycle.

Studies 7648 and 7927 enrolled nearly identical populations. Both studies employed Profasi as the active comparator. Study 7648 was conducted in Israel and six European countries. A total of 205 subjects were enrolled at nine university centers. Study 7927 enrolled 297 subjects and was carried out at 20 medical centers in the United States. Across the two studies, a total of 280 randomized subjects received Ovidrel. Study 7648 engaged a double-blind, double-dummy design whereas study 7927 was conducted as an open-label study. In study 7648, both Ovidrel and Profasi were administered subcutaneously while in study 7927 Ovidrel was administered subcutaneously and Profasi was administered intramuscularly. In study 7648, Ovidrel was administered at a dose of 250 micrograms and Profasi was administered at a dose of 5,000 IU while in study 7927, Ovidrel was administered at doses of 250 and 500 micrograms and Profasi was administered at a dose of 10,000 IU. In study 7648 nafarelin was utilized for down regulation while in study 7927 leuprolide was administered for down regulation. As a protection against potential bias, subjects were not randomized in either study until the day of hCG administration, after adequate follicular development was

documented. Subjects who exhibited excessive follicular development (estradiol levels higher than 5500 pmol/L or signs of the ovarian hyperstimulation syndrome) also were not randomized.

The double-dummy design of study 7648 provided an opportunity for a truly objective comparison between the recombinant and urinary-derived products while study 7927 provided comparisons between the two routes of administration, I.M. and S.C. and between the 250 microgram dosage and 500 microgram dosage of Ovidrel in a randomized open-label trial design.

In study 7648 it was clearly shown that Ovidrel 250 mcg was as effective as Profasi 5,000 IU for the induction of final follicular maturation and early luteinization in infertile women who had been appropriately pretreated with follicle stimulating hormone as part of an assisted reproductive technology program such as in vitro fertilization and embryo transfer. In study 7927, in a direct comparison of Ovidrel 250 mcg with Ovidrel 500 mcg, it was clearly shown that the 500 mcg dose of Ovidrel was equivalent in treatment efficacy to the 250 mcg dose of Ovidrel for the same indication. In a direct comparison of Ovidrel 250 mcg with Profasi 10,000 I.U., the 95% confidence intervals of the treatment difference in the primary efficacy endpoint between them was (-2.123, 2.003). This was within the clinically relevant range of ± 3 oocytes and demonstrated equivalent treatment efficacy. Based on the primary efficacy results of these two studies,

Study 8209 assessed the efficacy and safety of Ovidrel compared with Profasi for induction of ovulation. In study 8209, almost all subjects treated with Ovidrel 250 mcg ovulated. This was also true for those subjects treated with Profasi. Both products were effective and, statistically, Ovidrel was not inferior to Profasi.

Ovarian hyperstimulation syndrome is the most serious and potentially life-threatening condition associated with gonadotropin treatment. The ovaries are massively enlarged, and intravascular fluid volume shifts into the peritoneal space, resulting in hypovolemia, oliguria, hemoconcentration, and massive ascites. While OHSS may be unpredictable, it can usually be avoided by closely monitoring the patient and withholding hCG if ovarian response becomes excessive. In study 7648, one of 97 subjects receiving Ovidrel 250 mcg developed OHSS (1%). This was a mild event which did not require hospitalization. The occurrence of OHSS reported in study 7927 was quite different. Three

cases of OHSS (3.3%) occurred in the Profasi group (2 mild and 1 moderate). Three subjects receiving Ovidrel 250 mcg (3.2%) experienced mild or moderate OHSS, one serious case requiring hospitalization. However, eight subjects receiving Ovidrel 500 mcg (9.0%) experienced OHSS including 5 moderate and 2 severe events, three of them serious, requiring hospitalization. Thus, not only is the occurrence of OHSS with Ovidrel 500 mcg 2.8 times that of Ovidrel 250 mcg, the occurrence of serious cases of OHSS requiring hospitalization with Ovidrel 500 mcg is 3.1 times that of Ovidrel 250 mcg. Clearly, this study shows that the occurrence as well as the severity of OHSS is considerably greater with the use of Ovidrel 500 mcg than with Ovidrel 250 mcg. Since Ovidrel 500 mcg has been shown to be no more effective than Ovidrel 250 mcg, the increased occurrence and severity of OHSS associated with Ovidrel 500 mcg is another reason to avoid this dosage.

Three subjects receiving Ovidrel 250 mcg (3%) in study 8209, the ovulation induction study, also experienced OHSS. Only one of the subjects required treatment and none required hospitalization. Other factors which may have played a minor role in the great difference of the occurrence and severity of OHSS between subjects receiving Ovidrel 500 mcg and Ovidrel 250 mcg are 1) the higher median dose of FSH (2500 IU) administered in study 7927, where there was an Ovidrel 500 mcg study arm, than the median dose of FSH (2100 IU) in study 7648 where there was no Ovidrel 500 mcg study arm and 2) the fact that there was a higher number of follicles ≥ 10 mm on final ultrasound assessment before administration of hCG noted in study 7927 (13) than in study 7648 (11).

Multiple births are also of concern in patients treated for infertility with hCG. In ART, the risk of multiple births correlates with the number of embryos transferred and is usually higher than that seen with the use of hCG in ovulation induction. A total of 27 of 82 live deliveries (32.9%) resulted in multiple births in subjects receiving Ovidrel in the two ART studies. This is consistent with rates from ART practice. Two of 14 live deliveries (14.3%) resulted in multiple births in subjects receiving Ovidrel for ovulation induction. These two multiple births may be attributed directly to the pharmacologic action of FSH and hCG. While 14.3% is a high rate for natural conception, it is consistent with rates reported for anovulatory patients treated with FSH and hCG.

Congenital malformations are always of interest. Of a total of 119 clinical pregnancies occurring in subjects who received Ovidrel, three were associated with a congenital malformation of the fetus or newborn, all of which were judged by the investigators to be of unlikely or unknown relation to the Ovidrel. Each of the three malformations was distinctly different from each other. This 2.5% incidence of congenital

malformations does not exceed the incidence found in pregnancies resulting from either natural or assisted conception. It is highly unlikely that any of these malformation was caused by the Ovidrel.

The study designs are acceptable and the subject populations are appropriate. However, study 7927 could have been better designed as a double-blind, double-dummy study rather than an open-label study. The one additional placebo injection would not have been a large imposition on the subjects. An I.M. placebo for Profasi _____ in the United States. The primary efficacy endpoints are also appropriate. Ovidrel, which is recombinant human chorionic gonadotropin, will provide an alternative to urinary-derived human chorionic gonadotropin. Recombinant hCG should provide a constant product supply, absence of contaminants from human waste products, and a completely auditable manufacturing process.

Endometriomas can be confused with functional cysts. For this reason, studies 7648 and 7927 included subjects with mild endometriosis (AFS stage I or II), but excluded subjects with more severe endometriosis. Oocyte retrieval, even under ultrasound direction, may be more difficult in subjects with stage III or IV endometriosis. Both studies also excluded subjects with polycystic ovarian syndrome which was diagnosed, not by clinical examination, but by ultrasound criteria. This would exclude a large number of subjects who might otherwise be candidates for this treatment.

Down-regulation was confirmed in study 7648 by estradiol levels \leq 50 pg/mL, but in study 7927 down-regulation was confirmed by estradiol levels \leq 75 pg/mL which is unusually high. This discrepancy is acceptable. Calhaz (J Assist Reproduct Genet 1995; 12:615-9) has shown that when estradiol concentration was $<$ 100 pg/mL at the end of the pituitary desensitization phase, the degree of pituitary suppression had no effect on either the ovarian response to stimulation, the pregnancy rates, or the live birth rates. Dantas (Fertil Steril 1996; 65:122-6), and also Senoz (Gynecol Endocrinol 1995; 9:91-6) did not find any difference in treatment outcome when ovarian suppression at the start of the stimulation phase was less profound. Less profound pituitary suppression than usually considered adequate has no adverse effects on the ovarian response to gonadotropin stimulation and overall IVF results.

The primary variable in study 8209 was ovulation, which was defined as a single mid luteal phase serum progesterone level of \geq 9.4 ng/mL. Pulsatility in progesterone secretion could make interpretation difficult sometimes. However, by the mid luteal phase, the frequency of progesterone pulses is reduced and a pattern similar to the diurnal pattern of cortisol production is noted. Serial sampling might be expected to give

a more representative picture of corpus luteum function throughout the cycle, but a single mid luteal progesterone level of ≥ 9.4 ng/mL is acceptable to document ovulation since progesterone levels of > 3 ng/mL or > 4 ng/mL generally confirm an ovulatory cycle. Higher midluteal progesterone levels are usually seen in stimulated cycles (> 15 ng/mL) and were seen in study 8209, confirming high percentages of ovulation with both Ovidrel and Profasi.

Clinical pregnancies were a secondary endpoint in all three studies. This was defined as pregnancies during which a fetal sac and/or a fetal heart with activity was visualized by ultrasound on _____ Ectopic pregnancies were included as a clinical pregnancy. This is a liberal definition which is not accepted by some clinicians, but is accepted by others such as The Advanced Fertility Center of Chicago, Reproductive Science Center of the San Francisco Bay Area, Boca Fertility Peress Institute for Reproductive Medicine. Some clinicians define a clinical pregnancy as one with a pregnancy sac seen in the uterus on ultrasound, with fetal heart activity. Including as clinical pregnancies those with only a pregnancy sac and ectopic pregnancies is acceptable provided this definition accompanies any mention of the clinical pregnancy rate in labeling since this liberal definition would increase the clinical pregnancy rate. Since the same definition was applied to both the Ovidrel and Profasi arms of all three studies, one can reasonably compare the clinical pregnancy rates between both arms.

Ovidrel is well-tolerated and safe. Adverse events are not a problem. No clinically relevant drug-related trends for laboratory parameters or vital signs were identified. Anti-hCG antibodies are not a problem. Based on 125 clinical pregnancies following treatment, Ovidrel appears to have no causal deleterious effects on the offspring of subjects treated with it. Ovidrel is as effective as Profasi. The benefit-risk assessment yields an acceptable profile of safety for Ovidrel for both of its indications.

X. Postmarketing Clinical Studies:

No postmarketing clinical trials are required.

XI. Safety Update:

A 120-day Safety Update Report was received April 10, 2000. No new safety concerns are apparent. The incidence of adverse events remains essentially unchanged. A report of study 9073 is included which reports 84 subjects treated in Australia prior to IVF/ET and ICSI/ET. The adverse events reported in this study mirrors that reported in the studies

submitted in the original NDA submission. The report also includes the results of five ongoing pregnancies from study 8209. Table 9 in this review will be updated in the labeling to include the outcomes of these pregnancies.

XII. Labeling Evaluation:

The most important revision of the labeling recommended by FDA is the deletion of Ovidrel _____ as a recommended dosage for ART and the deletion of one vial of _____ Ovidrel _____ packaged together from the HOW SUPPLIED section. Revised draft labeling submitted August 14, 2000 is currently being rerevised by the sponsor as recommended by us.

XIII. Recommendation:

Approval of the application is recommended.

/S/

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

/S/

M.D.P.H.

9/15/00

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Safety Update Review

The safety update is included in Medical Officer review dated September 15, 2000, pages 43-44.

Ovidrel™ Team Leader Review

SEP 15 2000

NDA: 21-149

Drug: Ovidrel™ (Chorionic gonadotropin alfa)

Indication: Induction of final follicular maturation and early luteinization in infertile women who have been appropriately pretreated with follicle stimulating hormone (FSH) as part of an Assisted Reproductive Technology (ART) program

Dosage/Form/Route: 250 microgram (µg) sterile lyophilized powder to be reconstituted with 1 ml Sterile Water for Injection. A single dose is administered via subcutaneous injection once on the day following the last dose of FSH for an ART cycle or for ovulation induction.

Applicant: Serono Laboratories, Inc
Original Submission Date: November 24, 1999
Review Completed: September 1, 2000
Date of Memorandum: September 1, 2000

Background

The Agency has previously reviewed and approved two recombinant human FSH products (Gonal-F® and Follistim®) for use in controlled ovarian stimulation regimens in ART and ovulation induction. These recombinant gonadotropin products are produced by Chinese Hamster Ovary Cells that have been genetically engineered to produce the alpha and beta chains of the human FSH protein. These recombinant proteins offer high purity and specific activity, batch to batch consistency and are independent of the need to collect large amounts of human source materials.

Serono is the first sponsor to make an application for a recombinant human chorionic gonadotropin (r-hCG). Human chorionic gonadotropin (hCG) like hFSH and human luteinizing hormone (hLH) is composed of a single alpha subunit and a single target-specific beta subunit. The physiologic role of hCG is to support early pregnancy by prolonging the life of the corpus luteum and activating the secretion of estrogen and progesterone by this organ until this function is assumed by the placenta (about the 7th-10th gestational week). Because of the molecular similarity of hCG to hLH (the first 114 amino acids of the organ-specific beta chain of hCG shares 80% homology with the first 114 amino acids of the beta chain of LH) and because of the lack of a purified hLH product, hCG (derived from the urine of pregnant women) has been pharmacologically used as an LH analogue in both women and men. In women, hCG is used to

induce final follicular maturation and trigger ovulation in subjects receiving gonadotropins for controlled ovarian stimulation (COS).

The Sponsor proposes that r-hCG will provide an alternative to urinary-derived human chorionic gonadotropin (u-hCG) for injection (Profasi®). In support of this NDA application, Serono has submitted three Phase 3 studies (two to support the indication for use in ART and one to support the indication for use in ovulation induction). One of the ART studies was conducted in the United States under IND 48,934, and submitted September 29, 1995. NDA 21,149 was submitted November 24, 1999. The study report for Protocol 8209 for ovulation induction was not submitted until 1/13/00 prior to the filing date of January 23, 2000.

Chemistry/Manufacturing

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

r-hCG is produced in genetically engineered Chinese Hamster Ovary Cells in which the genes coding for the alpha and beta subunits of hCG were introduced through recombinant DNA technology. During the production phase, r-hCG

Ovidrel™ is a sterile lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (1ml). The vials are filled (285 µg) based on mass, instead of units traditionally used for the manufacturing of gonadotropin drug products.

The drug substance is manufactured by Laboratoires Serono, S.A. (LSA). The manufacturing facility complies with cGMP. The proposed specifications and analytical methods to assess quality control were considered to be satisfactory.

Serono Pharma S.P.A. in Italy manufactures the drug product. The drug product is packaged at Serono Laboratories, Inc, USA. These facilities are both in compliance with cGMP. All analytical methods to assess quality control were deemed suitable for regulatory purposes.

Based on the primary as well as the supportive stability data, 24-month expiry is granted. The reconstituted solution is stable for 24 hours at 25°C.

The NDA was recommended for approval from the perspective of Microbiology. The NDA is considered acceptable for approval from a Chemistry, Manufacturing and Controls point of view.

Product Name

The tradename Ovidrel™ was recommended for acceptance by OPDRA on June 27, 2000.

Pre-clinical Pharmacology and Toxicology

On the basis of the pre-clinical safety evaluation, Pharmacology recommends that from a pre-clinical point of view the NDA is acceptable for approval. The pregnancy category should be X based on the reprotoxicity data. Intrauterine death and impaired parturition were observed in pregnant rats given 500 IU/day, which is equivalent to 3 times the maximum human dose (10,000 IU).

Biopharmaceutics

The pharmacokinetics and bioavailability of r-hCG was addressed in 6 studies submitted to the NDA. The following observations and conclusions were made.

Following subcutaneous administration of Ovidrel™, the maximum serum concentration is reached after approximately 12–24 hours. The mean bioavailability of Ovidrel™ following a single subcutaneous injection is about 40 %. The steady state volume of distribution and the total clearance are 5.9 ± 1.0 and 0.29 ± 0.04 L/h, respectively. After subcutaneous administration of Ovidrel™, hCG is eliminated from the body with a terminal half-life of about 29 hours. One tenth of Ovidrel™ is excreted in the urine. The relationships of the pharmacokinetic effects of Ovidrel™ to pharmacologic effects of Ovidrel™ are complex and vary with the pharmacodynamic marker examined. In general, pharmacologic effects are not proportional to exposure and in some cases appear to be near maximal at the 250 µg dose. In subjects undergoing IVF-ET given Ovidrel™ to trigger ovulation, the results of a population PK/PD analysis generally support the data obtained in healthy subjects. Pharmacokinetics, safety and efficacy have not been established in subjects with renal or hepatic insufficiency.

From a Biopharmaceutics perspective, the NDA is acceptable for approval.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

The evaluative report of the clinical inspections for NDA 21-149 summarized inspections at two sites for Study 7927 and one site each for Study 7648 and Study 8209. All of these sites were found to be acceptable and no violations were found that would negatively impact the reliability or integrity of the data submitted in the NDA.

Clinical Efficacy and Safety

Study 8209 (ovulation induction)

Study 8209 was a Phase 3, double-blind, double-dummy, multicenter non-inferiority design study conducted in Europe, Australia and Israel to compare the safety and efficacy of r-hCG (Ovidrel™ 250 µg) to u-hCG (Profasi® 5000IU) in anovulatory infertile women undergoing stimulation of follicular development with Gonal-F® (recombinant human FSH [r-hFSH]). A low dose administration regimen was followed for ovarian stimulation. Recombinant human FSH was started (stimulation day 1) at a dose of 75 IU (administered SC) between cycle day 3 and 5 of a spontaneous or induced menstrual bleed. The starting dose was maintained for the first 14 days of stimulation (unless criterion for administration of hCG was met), then if ovarian response was lacking a dose increase of 37.5 IU was allowed. Subsequent similar dosage increases were allowed every 7th treatment day (i.e. stimulation days 22 and 29). Randomization in a 1:1 fashion to either 250 µg of r-hCG SC (n=99) or 5000 IU of u-hCG SC (n=99) occurred after assessment for adequate follicular development. The follicular development was judged as adequate (and appropriate) when one follicle reached a mean diameter of ≥ 18 mm with not more than 3 others with a mean diameter ≥ 16 mm and not more than 4 follicles with a mean diameter between 11 and 14 mm. Estradiol (E₂) levels were to be within an acceptable range for the number of follicles present, but not higher than 5500 pmol/L (1500 pg/ml).

The primary efficacy analysis was the proportion of subjects who ovulated based on a serum progesterone (P_4) level ≥ 30 nmol/L (9.4 ng/ml). This reviewer feels that this definition of ovulation is not an adequate assessment of ovulation for a gonadotropin stimulation cycle. Usually a P_4 level ≥ 15 ng/ml is obtained with gonadotropin stimulation and, therefore, this cutoff value would have better represented appropriate ovulation for a gonadotropin-stimulated cycle. Nevertheless, the Sponsor applied this criterion to both treatment arms. In the Sponsor's original analysis non-inferiority was declared if the 1-sided 95% confidence interval of the difference between r-hCG and u-hCG did not exceed 20% in favor of u-hCG. For the ITT group, the proportion of subjects who ovulated was 91.9% in the r-hCG group and 85.9% in the u-hCG group. The estimate of the treatment effect of taking r-hCG rather than u-hCG was +6.0 with a lower limit of the 1-sided 95% CI for the treatment effect of -3.7%. This is acceptable as demonstrating efficacy under this analysis as the clinically acceptable limit was -20%. The Sponsor was asked by the clinical reviewing team to perform another analysis with the use of a 2-sided 95% CI. The Agency generally requires a 2-sided 95% CI of the treatment difference to establish equivalence of two treatments or a 1-sided 97.5% CI of the treatment difference to establish non-inferiority of one treatment to the other. In the Sponsor's new analysis, the lower limit of the 2-sided 95% CI of the treatment effect was -3.4%, which was within the acceptable -20% and thus demonstrated efficacy. The secondary efficacy parameters of midluteal P_4 (78.4 nmol/l for r-hCG vs. 55.75 nmol/l for u-hCG), ultrasound visualization of ovulation, and serum hCG levels were all consistent with the non-inferiority of the recombinant hCG product to the urinary hCG product.

Clinical pregnancy (defined in this NDA as the presence of a fetal sac regardless of absence or presence of the fetal heartbeat) was determined in 22 r-hCG subjects and 29 u-hCG subjects. The proportion of subjects achieving clinical pregnancies was not statistically different between those receiving the r-hCG and those treated with the u-hCG. This reviewer takes some exception with a definition of clinical pregnancy based on the demonstration of a fetal sac (without a fetal heart beat). While in the broadest since this represents verification of pregnancy based on more criteria than a positive biochemical test (i.e. positive serum hCG) alone, the presence of the fetal sac without notation of the fetal heart beat does not allow any assessment of the viability of that pregnancy. Also extra-uterine pregnancies were included as clinical pregnancies which I also find unacceptable. In the context of treatment for infertility (as it is for all desired pregnancy) it is important to the patient not just that a pregnancy is achieved but that this be a viable pregnancy. Nevertheless, consistent criteria were applied to both recombinant and urinary products and the data support that the recombinant product is not inferior to the urinary product under this definition. Of note, compared to the u-hCG group, the r-hCG group had a greater proportion of clinical pregnancies not reaching term (31.8% r-hCG vs. 17.2% u-hCG) $p=0.244$ and a lower rate of ongoing and delivered pregnancies (68% r-hCG vs. 83% u-hCG). None of these differences were statistically significant. There was a 14.3% multiple birth rate with r-hCG and 15.0% with u-hCG.

One subject treated with r-hCG had a baby with a 47 XXX karyotype that was noted upon prenatal amniocentesis. Both the subject and her husband were noted to have a normal karyotype. One subject treated with u-hCG had a twin gestation that resulted in the still birth of one of the twins and premature birth at 25 weeks gestational age and subsequent neonatal death of the second twin.

The most frequent adverse events reported after administration of hCG in the women themselves were application site disorders including pain, inflammation, bruising and reaction. A statistically significant lower proportion of r-hCG subjects (9%) reported at least one injection site symptom compared to u-hCG (31%). Ovarian hyperstimulation syndrome

(OHSS) was reported in three subjects treated with r-hCG compared to none treated with u-hCG. None of the three subjects required hospitalization. One of the three subjects became pregnant during the treatment.

Study 8209 demonstrated that 250 µg of r-hCG was effective in inducing final follicular maturation and early luteinization in an ovulation induction regimen and that this dose was safe and well tolerated

Study 7648 (ART)

Study 7648 was a Phase 3, double-blind, double-dummy, multicenter study, with a non-inferiority design, conducted in Europe and Israel to compare the safety and efficacy of r-hCG (Ovidrel™ 250 µg) to u-hCG (Profasi® 5000IU) in women undergoing pituitary desensitization with nafarelin and controlled ovarian stimulation with r-hFSH (Gonal-F®) as part of an IVF/ET cycle. Subjects received 400 µg of nafarelin twice daily for at least 10 days to effect down-regulation. When down-regulation was confirmed ($E_2 \leq 50$ pg/ml, endometrial thickness ≤ 10 mm and no ovarian activity on ultrasound), r-hFSH was administered SC once daily. The starting dose of r-hFSH could vary in accordance with the normal practice of the study center and the subject's history. The dosage was also adjusted according to ovarian response with a maximum dose of 450 IU/day and a maximum total cumulative dose not to exceed 7500 IU. This is consistent with usual practice. Nafarelin and r-hFSH were co-administered until the criterion for hCG administration had been met. Randomization in a 1:1 fashion to either 250 µg of r-hCG SC (n=99) or 5000 IU SC of u-hCG (n=99) occurred after assessment for adequate follicular development. The follicular development was judged as adequate (and appropriate) when one follicle reached a mean diameter of ≥ 18 mm and at least 2 follicles reached a mean diameter ≥ 16 mm and the E_2 level was approximately 150 pg/ml/follicle.

The primary efficacy analysis was the number of oocytes retrieved per subject receiving r-hCG or u-hCG. In the ITT analysis of the Sponsor, the mean number of oocytes retrieved per subject was 10.609 in the 250 µg r-hCG group and 10.621 in the 5000 IU u-hCG group with a treatment effect of -0.011 and a 2-sided 90% CI for the treatment effect of (-1.206, +1.183). The Sponsor was asked by the clinical reviewing team to perform an analysis with a 2-sided 95% CI for the treatment effect and this was (-1.437, 1.414). In both analyses, the confidence intervals were within the clinically acceptable range of ± 3 oocytes and thus it can be concluded that the two treatments are equivalent. Treatment with r-hCG vs. u-hCG showed no statistical differences in the secondary efficacy parameters of mean number of mature oocytes retrieved per subject ($p=0.0668$), mean number of 2 PN fertilized oocytes per subject ($p=0.6032$), mean number of 2 PN or cleaved embryos per subject ($p=0.2563$), implantation rate per embryo transferred ($p=0.2539$) or mean mid-luteal serum progesterone levels ($p=0.0655$).

The clinical pregnancy (fetal sac \pm fetal heart beat) rate per initiated treatment cycle was 33% (n=32) for the 250 µg r-hCG group and 24.7% (n=23) for the 5000 IU u-hCG group, $p=0.1920$. The difference was not statistically different. As with the Study 8209, I take exception with this more liberal definition of clinical pregnancy that does not require the presence of a fetal heartbeat. In addition, Study 7648 and Study 7927 (to be discussed below) are ART studies and the ART registry data published by the Society of Assisted Reproductive Technology (SART) in conjunction with the Centers for Disease Control (CDC) define clinical pregnancy as intrauterine pregnancy with fetal heart beat. The label presenting the

data from these studies will have to clearly state how clinical pregnancy was defined for these studies. The proportion of clinical pregnancies not reaching term was not statistically different between r-hCG (19%; n=6) and u-hCG (9%, n=2). The live birth rates were also similar (r-hCG = 81.2% and u-hCG =91.3%). There were 30.8% twin gestations in the r-hCG group and 38.1% in the u-hCG group.

There were three serious fetal/neonatal adverse events noted in r-hCG-treated subjects. These included a neonatal death at 6 days from severe asphyxia, an anencephalic fetus terminated at 16 weeks gestation and a complete abortion of a twin gestation after notation of fetal heartbeat. There were four fetal/neonatal serious adverse events in three u-hCG-treated subjects. These included a neonatal death from beta hemolytic streptococci infection, a congenital heart defect and right arm malformation noted in a fetus at 19 weeks of gestation that subsequently delivered, and an extra-uterine pregnancy.

The most frequent adverse events reported after administration of hCG in the women themselves were application site disorders including pain, inflammation, bruising and reaction. A significantly higher proportion of subjects noted local inflammation and pain after treatment with u-hCG (20%-24%) than after treatment with r-hCG (3-7%). There were 7 severe or life threatening adverse events occurring after hCG administration. These included one case of pancreatitis and one carcinoma of the cervix in subjects who had been administered r-hCG. Both of these events were designated as unrelated to hCG. There was one case of severe OHSS judged as related to study medication, one case of appendicitis and three cases of severe injection site pain in the u-hCG group.

Study 7648 demonstrated that 250 µg of r-hCG was effective in inducing final follicular maturation and early luteinization in subjects who had received pituitary sensitization and COS in an ART regimen and that this dose was safe and well tolerated.

Study 7927 (ART)

Study 7927 was a Phase 3, open-label, multicenter study, with an equivalency design, conducted in the United States to compare the safety and efficacy of r-hCG (Ovidrel™ 250 µg and 500 µg SC injection) to u-hCG (Profasi® 10,000 IU IM injection) in women undergoing pituitary desensitization with leuprolide acetate and controlled ovarian stimulation with highly purified urinary human FSH (Fertinex™) as part of an IVF/ET cycle. Subjects received 1 mg of leuprolide acetate daily by SC injection to effect down-regulation. When down-regulation was confirmed ($E_2 \leq 75$ pg/ml), the dose of leuprolide acetate was decreased to 0.5 mg daily and continued along with the urinary human FSH (u-FSH) up to and including the day of hCG administration. Treatment with u-FSH started at a dose of 225IU/day for the first five days of treatment and at the discretion of the investigator adjusted by increments of 75 to 150 IU/day every 2 to 3 days according to ovarian response. The maximum dose of u-FSH allowed per day was 450 IU and the cumulative dose could not exceed 6,000 IU. Randomization in a 1:1:1 fashion to either 250 µg of r-hCG SC (n=94), 500 µg of r-hCG SC (n=89), or 10,000 IU IM of u-hCG (n=92) occurred after assessment for adequate follicular development. The follicular development was judged as adequate (and appropriate) when one follicle reached a mean diameter of ≥ 18 mm and at least 2 follicles reached a mean diameter ≥ 16 mm and the E_2 level was judged as adequate for the number of follicles present.

The primary efficacy analysis was of the number of oocytes retrieved per subject receiving r-hCG or u-hCG. The analysis of the Sponsor compared 500 µg r-hCG to 10,000 IU u-hCG and

250 µg r-hCG to 500 µg r-hCG and used a 90% CI on the difference between the two pairs of treatment groups. The treatment pair was declared to be equivalent if the limits of the 90% CI fell within the clinically relevant range of ± 3 oocytes. In the ITT analysis of the Sponsor, the mean number of oocytes retrieved per subject was 13.60 in the 250 µg r-hCG group, 14.64 in the 500 µg r-hCG group and 13.66 in the 10,000 IU u-hCG group. For the comparison of the 500 µg r-hCG to 10,000 IU u-hCG, the mean difference was 0.98 with a 90% CI of (-0.775, 2.729) and the treatments were declared to be equivalent. For the comparison of the 500 µg r-hCG to 250 µg r-hCG, the mean difference was 1.04 with a 90% CI of (-0.706, 2.781) and the treatments were declared to be equivalent. The Sponsor was asked by the clinical reviewing team to perform an analysis comparing the 250 µg r-hCG group to the 10,000 IU u-hCG group utilizing a 2-sided 95% CI. The treatment difference was -0.06 with a 95% CI of (-2.123, 2.003) and thus the treatments are considered equivalent as the confidence intervals fall in the clinically acceptable range of ± 3 oocytes. No statistical difference was observed between the 250 µg r-hCG group or 500 µg r-hCG group and the 10,000 IU u-hCG group for the secondary parameters of mean number of mature oocytes retrieved per patient, mean number of 2 PN fertilized oocytes per patient, mean number of 2 PN or cleaved embryos per patient, implantation rate per embryo transferred and mean mid-luteal serum progesterone levels. However, there were statistically significant differences between the 250 µg r-hCG group and the 500 µg r-hCG group in the parameters of mean number of 2PN fertilized oocytes per patient, the mean number of 2 PN or cleaved embryos per patient and the mean mid-luteal serum progesterone levels in favor of the 500 µg r-hCG group. These differences were not born out in the implantation rates and clinical pregnancy rates for the two groups.

The clinical pregnancy (fetal sac \pm fetal heart beat) rate per initiated treatment cycle was 35% (n=33) for the 250 µg r-hCG group, 36% (n=32) for the 500 µg r-hCG group and 35.9% (n=33) for the 10,000 IU u-hCG group. The difference was not statistically different between the 250 µg r-hCG group and the 10,000 IU u-hCG group and between the 500 µg r-hCG group and the 10,000 IU u-hCG group. The proportion of clinical pregnancies not reaching term was not statistically different between any of the analyzed treatment group pairs (250 µg r-hCG vs. 10,000 IU u-hCG, 500 µg r-hCG vs. 10,000 IU u-hCG and 250µg r-hCG vs. 500 µg r-hCG). The live birth rates were also similar (250 µg r-hCG = 87.9%, 500 µg r-hCG=84.4% and 10,000 IU u-hCG =84.9% %). There were 31.1% and 37.0 % multiple gestations in the 250 µg r-hCG group and the 500 µg r-hCG groups, respectively and 50.0 % in the 10,000 IU u-hCG group.

There were 7 serious fetal/neonatal adverse events noted in the study. Five of these were ectopic pregnancies (one in the 250 µg r-hCG group, two in the 500 µg r-hCG group and two in the 10,000 IU u-hCG group. There was one triplet gestation in the 500 µg r-hCG group group, where one of the fetuses was diagnosed with Down's syndrome and atrial septal defect. There was also an apparent cord accident and stillbirth of one twin (male) of a twin gestation in the 10,000 IU u-hCG group. The remaining twin, a girl, was born healthy.

The most common adverse events were post-operative pain, nausea, abdominal pain, and OHSS. These events all occurred more frequently in the 500 µg r-hCG group than in the other treatment groups. OHSS was reported in 3.2% (n=3) in the 250 µg r-hCG group, 9.0% (n=8) in the 500 µg r-hCG group and 3.1% (n=3) in the 10,000 IU u-hCG group. OHSS as a severe event was also reported more in the 500 µg r-hCG group (3.4%) than in the 250 µg r-hCG group (1.1%) or the 10,000 IU u-hCG group (0%). Two of the subjects with severe OHSS in the 500 µg r-hCG group had to discontinue the study due to the event. There was one case

each of ovarian torsion, vasovagal reaction and abdominal pain in subjects receiving r-hCG. The three groups were similar with regard to incidence of overall injection site disorders. However, severe bruising was reported in one patient in the 250 µg r-hCG group and severe pain was reported in three subjects in the 250 µg r-hCG group and two subjects in the 500 µg r-hCG group. Increased ALT levels were observed in 6.4% of the 250 µg r-hCG group, 10.1% of the 500 µg r-hCG group and 11.9% of the u-hCG group after correction for pre-existing conditions.

One criticism of the design of this study is that unlike the previously discussed Phase 3 studies which were conducted outside of the U.S., the Sponsor chose not to blind participants and investigators to the treatment groups thus missing the opportunity to have a truly objective study. The Sponsor argues that performing a sham injection is unethical which is certainly arguable. The Sponsor further argues that blinding offers no apparent advantage when objective endpoints are used. While the use of objective endpoints may allow for less reliance on blinding, one might question whether the number of oocytes retrieved is a truly objective endpoint since it would depend on the investigator/clinician to make sure that all follicles judged to be appropriately developed are punctured for retrieval. Nevertheless, even with this shortfall in study design, Study 7927, supported Study 7648 in establishing the efficacy of 250 µg of r-hCG in inducing final follicular maturation and early luteinization in subjects who had received pituitary sensitization and COS in an ART regimen. This dose of r-hCG was also demonstrated to be safe and reasonably tolerated. The 500 µg dose of r-hCG also was effective, but had a more adverse safety profile particularly with respect to OHSS. Therefore, the lowest effective dose demonstrated was the 250 µg dose of r-hCG.

Discussion and Conclusions

Study 8209 and Studies 7648 and 7927 establish the efficacy of the 250 µg dose of r-hCG as the lowest effective dose for inducing final follicular maturation and early luteinization in an ovulation induction regimen or in infertile women who have had pituitary desensitization and who have been appropriately pretreated with a FSH as part of an ART program such as IVF-ET. The definition of clinical pregnancy used by the Sponsor in establishing these rates of pregnancy will be clearly defined in the label. The 250 µg dose of r-hCG is associated with an acceptable safety profile. The rate of OHSS, which was acceptable, will be clearly listed in the label. Three congenital malformations were noted in the 119 clinical pregnancies (across all treatment groups). This rate of 2.5% is not substantially different from the background 2% rate of congenital malformation. Finally, information on the modest rise in ALT (hepatic transaminase) will be added to the Precautions section of the Ovidrel™ label. After exclusions of pre-existing conditions, elevations in ALT up to 1.2 times the upper limit of normal were found in 3% of 335 subjects treated with the 250 µg dose of r-hCG, 10% of 89 subjects treated with the 500 µg dose of r-hCG and 4.8% of 328 subjects treated with u-hCG. The number of subjects reflect the total safety base from Studies 7927, 7648, 8209 and 9073 (not submitted in this NDA) for each treatment group. Likewise, information on the rise in ALT for subjects treated with u-hCG should also be added to the label of the u-hCG products.

I concur with the recommendation of all the reviewing disciplines that this NDA should be approved.

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

9/15/00

cc: Division File NDA 21-149

S. Allen, MD

M. Mann, MD

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E. Deguia

S. Slaughter, M.D., Ph.D.

**Attachment A
Non - U.S. Investigator List
Financial Certification**

Study 8209

Investigator	Center Number	Country
<i>(PI = Principal Investigator)</i>		
	4	France
	11	Spain
	8	Germany
	19	Israel
	12	UK
	18	Israel
	17	Switzerland
	1	Australia
	1	Australia
	13	UK
	17	Switzerland
	5	France
	9	Italy
	3	Canada
	6	France
	8	Germany
	15	UK
	18	Israel
	11	Spain
	3	Canada
	20	UK
	1	Australia
	5	France
	12	UK
	1	Australia
	10	Italy
	6	France
	15	UK
	2	Australia
	13	UK
	1	Australia
	16	Germany
	16	Germany
	1	Australia
	14	Australia
	16	Germany
	1	Australia

Attachment B

**List of Investigators
for whom Due Diligence was Performed but Disclosure was not Obtainable**

Study 8209

Center Number	Investigator	Number of Patients Enrolled	Country	Reason for Not Obtaining Disclosure
21		0	France	This investigator did not enroll any patients
10		14	Italy	No response
2		6	Australia	Retired