

Medical Officer's Original Clinical Review

NDA Number: 21-322
Name of Drug: Luveris™
Applicant: Serono, Inc.
Date Submission Received: May 1, 2001
Draft Review Completed: February 19, 2002
Date Review Finalized: February 25, 2002

EXECUTIVE SUMMARY:

- I. Recommendations:
 - A. Approval of this application is not recommended from a clinical perspective based on the failure of demonstration of efficacy in clinical trials.
 - B. Recommended Phase 4 Studies:

Followup of children born to all treated study patients should be conducted and reported to FDA.
- II. Summary of Clinical Findings:
 - A. At the pre-IND meeting May 21, 1992, it was agreed that two clinical dose-finding studies of equal size and using the same protocol, one in the United States (study 6905) and one in Europe (Study 6253) would be conducted in women diagnosed with WHO Group I anovulation (idiopathic hypogonadotropic hypogonadism), a rare condition estimated by the applicant to be 14,740 cases per year in the United States. There were to be 32 patients in each study, based on the rarity of the condition rather than on statistical considerations.

IND 44,108 was submitted December 8, 1993 with only the protocol for the U.S. study (6905) submitted. An amendment to the protocol was submitted July 20, 1994 before the start of the study. Three significant revisions were made in the "Inclusion Criteria" to make the study population more closely match the varied endocrine profile of hypogonadotropic patients treated in clinical practice in the U.S. These revisions were:

1. The need to have a negative progesterone challenge test during the screening procedure was deleted and in its place the requirement for an estradiol level less than 60 pg/ml was added.
2. The requirement of an FSH below 5 IU/L was deleted and replaced by the requirement for the FSH to be at or below the 50th percentile of normal range for the follicular phase established by the central laboratory (≤ 10.85 IU/L).
3. The requirement of an LH below 5 IU/L was deleted and replaced by the requirement for the LH to be at or below the 50th percentile of normal range for the follicular phase established by the central laboratory (≤ 13.3 IU/L).

The requirement of an LH < 1.2 IU/L was never in protocol 6905.

No mention was ever made regarding the European study and the European protocol was not submitted until June, 1998 when the study was completed. Even though it had been agreed in the pre-IND meeting that both U.S. and European studies would be identical, the European study entered only subjects with a screening LH of < 1.2 IU/L. Thus the population studied in the two trials were different. Serono now states that they believe that women with hypogonadotropic hypogonadism and low LH levels (< 1.2 IU/L) require LH supplementation and deserve the option to choose an all recombinant gonadotropic therapy. This seems to imply that such patients with LH levels above 1.2 do not require LH supplementation. The first annual report to the IND in 1996 stated that the U.S. study would provide the primary safety and efficacy data for a full NDA. The second annual report submitted in 1997 stated that the U.S. study would become the basis for an NDA. A request for orphan drug status, subsequently approved, was submitted January 14, 1994.

In the pre-NDA briefing document submitted June 12, 1998, the proposed indication was stated as "treatment of women with chronic anovulation due to hypogonadotropic hypogonadism (H.H.)." The sponsor requested that the

Agency confirm that the data from studies 6253 (European) and 6905 (U.S.) were adequate for filing and approval of an NDA for the proposed indication. In this briefing document study, 6253 was referred to in the "Introduction" as pivotal while study 6905 was not. Only studies 6253 and 6905 were mentioned and data only from these two studies were submitted.

The primary efficacy endpoint for both studies was "follicular development" defined by three parameters, all of which had to occur, including a midluteal progesterone level indicative of ovulation.

The results of study 6905 revealed 25 IU of Luveris™ to be numerically better than 75 IU of Luveris™ and placebo to be almost as efficient as 75 IU of Luveris™. Clearly, in the patient population studied, Luveris™ was not shown to be effective in treating H.H. as usually diagnosed in the U.S. A total of 40 subjects received treatment.

The results of study 6253 revealed 75 IU of Luveris™ to be numerically better than 25 IU of Luveris™ and better than placebo in a population of profoundly FSH and LH deficient H.H. patients. These findings were based on a total of 38 patients with screening LH < 1.2 IU/L.

An analysis of a subset of patients in study 6905 who had a screening LH of less than 1.2 IU/L failed to confirm the findings of study 6253. It showed 25 IU of Luveris™ to be numerically better than 75 IU of Luveris™. A total of 15 subjects were analyzed in this subset of patients.

The fileability of the proposed NDA was discussed with the Director and Deputy Director, Office of Drug Evaluation II and the Deputy Director, Center for Drug Evaluation and Research October 21, 1998, who agreed that if the NDA were submitted, it would not be fileable.

On November 18, 1998 the sponsor informed the Division of new data from two additional clinical trials carried out in Europe. Study 7798 was conducted in Germany in a profoundly LH – deficient population (LH \leq 1.2 IU/L) while study 8297 was conducted in Spain in a moderately LH deficient population (LH below or within normal range). Neither study employed a dose of LH below 75 IU and both are submitted as supportive of the 75 IU dosage.

The sponsor stated that "Recent studies have identified the profoundly LH – deficient patients (LH < 1.2 IU/L) as the most appropriate population for demonstrating the therapeutic benefit of exogenous LH". The reference listed was one 1991 publication by Shoham of 9 patients which was published long

before the initial IND was submitted for study of patients which allowed inclusion of subjects with higher LH levels. Shoham did not study patients with LH > 1.2 IU/L.

On February 23, 1999 the applicant was informed that they should conduct a phase 3 trial comparing 75 IU of Luveris™ with placebo in patients with LH levels less than 5 IU/L, including a significant number of patients with a screening LH level less than 1.2 IU/L, all of whom desired pregnancy. The primary clinical endpoint should be ovulation rates. The results of this study (study 21008) showed that 66.7% of patients receiving 75 IU of Luveris™ experienced follicular development while 20.0% of patients receiving placebo did so. The applicant had expected that an effective dose of Luveris™ would result in follicular development occurring in 90% of the treated patients.

A total of five clinical trials in which a total of 173 subjects were entered provide the data for clinical evaluation in this application.

B. Efficacy:

Clinical studies have not demonstrated the efficacy of Luveris™ in association with r-hFSH for the induction of ovulation in infertile patients with profound LH and FSH deficiency. The treatment effect was not clinically or statistically significantly substantial.

C. Safety:

Safety testing is adequate. The number of patients treated is small and the safety database is not large. However, the indication is for an orphan drug indication, which is rare. No unexpected adverse events were reported and none are expected. There is considerable safety known about menotropins which contain urinary – derived LH and FSH.

No reliable drug/drug interaction studies have been conducted.

D. Dosing:

The dose of 75 IU/ day has not been established as the minimum effective dose. A dose of 25 IU/day may be sufficient. There is no evidence that a dose higher than 75 IU/day is more effective than 75 IU/day and the studied dose of 225 IU/day has the potential for being unsafe. The use of Luveris™ in H.H. patients with screening LH levels higher than 1.2 IU/L has been shown to be ineffective.

E. Special Populations:

Luveris™ is being indicated for ovulation induction, an indication that is applicable only to females. It is not indicated for use in pediatric patients and safety and efficacy in such patients have not been established. Clinical studies did not include patients over the age of 39 years. This drug is contraindicated in pregnancy. The safety and efficacy of the drug in renal and hepatic insufficiency have not been studied. The vast majority of patients studied were Caucasian. Racial and ethnic differences are not likely to be of any significant concern regarding efficacy or safety of the drug product.

CLINICAL REVIEW:

I Introduction and Background:

- A. Established Drug Name: Lutropin alfa for injection
- B. Proposed Trade Name: Luveris™
- C. Therapeutic Class: Infertility
- D. ATC Classification: ATC G03 GA Gonadotropins
- E. Applicant's Proposed Indication: For concomitant administration with recombinant human follicle stimulating hormone (r-hFSH) for the induction of ovulation in infertile women with severe LH and FSH deficiency.
- F. Applicant's Proposed Dosage: 75 IU daily. Treatment duration should not normally exceed 14 days unless signs of imminent follicular development are present. Should be administered concomitantly with r-hFSH, 75 to 150 IU per day. To complete follicular development and effect ovulation in the absence of an endogenous LH surge, 5,000 or 10,000 USP units of human chorionic gonadotropin (hCG) should be given one day after the last dose.
- G. Age Groups Studied: 18-39 years of age.
- H. Relevant Facts: In a pre-IND meeting May 21, 1992 the applicant stated that they intended to request designation of recombinant human

lutinizing hormone (r-hLH) as an orphan drug product for the treatment of women with chronic anovulation due to hypogonadotropic hypogonadism (H.H.). No application for marketing had been submitted to any country at that time. The applicant's clinical consultant made it clear that only a small dose of r-hLH would be needed for treatment.

In the pre-IND meeting it was agreed that two clinical studies of equal size using the same protocol, one in the U.S. and one in Europe, would be performed in women diagnosed with WHO Group I anovulation. These are women with amenorrhea, little or no evidence of endogenous estrogen activity, low or unmeasurable serum and urinary gonadotropins, and who do not respond with withdrawal bleeding when a suitable progestational agent is administered. Thirty-two subjects were to be in each study.

The IND was submitted December 8, 1993 with only the protocol for the U.S. study (6905) submitted. The study was entitled, "An open, randomized, dose-finding multicenter study to determine the minimal effective dose and to assess the safety of r-hLH to support r-hFSH – induced follicular development in anovulatory women with hypogonadotropic hypogonadism". No mention was made of the European protocol. It was stated that at the present time human menopausal gonadotropins containing equal quantities of hLH and hFSH remain the standard indicated therapy for infertility due to WHO Group I anovulation. While it was agreed in the pre-IND meeting that the dose of r-hFSH would be a fixed dose of 75 IU/d throughout the whole cycle, it was noted that the submitted protocol fixed this dose at 150 IU/d.

The initial protocol required all subjects to have FSH and LH < 5 IU/L and to have a negative progesterone challenge test.

Amendment 1 was submitted to the IND July 20, 1994 before the start of the study. Three significant revisions were made to the "Inclusion Criteria" to make the study population more closely match the varied endocrine profile of hypogonadotropic patients treated in clinical practice. This followed strong investigator input after review of their patient files.

These three revisions of the U.S. protocol were:

1. The need to have a negative progesterone challenge test during the screening procedure was deleted and in its place the requirement for an estradiol level less than 60 pg/ml was added.

2. The requirement of an FSH below 5 IU/L was deleted and replaced by the requirement for the FSH to be at or below the 50th percentile of normal range for the follicular phase established by the central laboratory (< 10.85 IU/L).
3. The requirement of an LH below 5 IU/L was deleted and replaced by the requirement for the LH to be at or below the 50th percentile of normal range for the follicular phase established by the central laboratory (< 13.3 IU/L).

Orphan drug designation was granted October 7, 1994.

The European study began in September, 1993 and the U.S. study started in July, 1994. The General Investigational Plan submitted in the first annual report May 15, 1996 stated, "Study 6905 (i.e. the U.S. study) will provide the primary safety and efficacy data — for a full NDA". The General Investigational Plan submitted in the second annual report May 16, 1997 stated, "Study 6905 will become the basis for an NDA". On June 12, 1998 the sponsor submitted a pre-NDA package that included evaluable patient results of the U.S. study (6905) which was conducted under the IND and evaluable patient results of the European study (6253) which was conducted under GCP principles. While the sponsor stated that the studies were generally similar, there appeared to be significant differences in them. The question posed to the FDA was, "Are the safety and efficacy data from the clinical information presented adequate to support the filing, and subsequent approval, of an NDA for the proposed orphan drug indication?"

In study 6905, there was one primary efficacy variable (follicular development) defined by 3 criteria (at least one follicle with a mean diameter ≥ 17 mm, and a preovulatory estradiol serum level ≥ 160 pg/mL, and a midluteal progesterone level ≥ 10 ng/mL. No statistically significant effect of addition of r-hLH was demonstrated on the primary efficacy endpoint or on any one of the 3 criteria analyzed separately in evaluable subjects. Study 6905 contained the traditional population of hypogonadotropic hypogonadism that is treated in the U.S. The study confirmed that some patients with H.H. may respond to FSH alone.

In study 6905, the follicular development rate was 55.6% in the FSH-alone group. This could be interpreted as indicating that exogenous LH is not required for most H.H. patients.

Study 6253 contained a more strictly defined population of profoundly gonadotropin deficient patients. A statistically significant dose – related trend to achieving follicular development, the primary efficacy endpoint, was reported in evaluable subjects by the sponsor.

One subject in study 6253 became pregnant during the first cycle of treatment while receiving FSH – alone (chemical pregnancy).

Had the optimal dose of r-hLH been determined? In study 6905, the best response for follicular development was with the 25 IU r-hLH dose. In study 6253, the 75 IU and 225 IU doses were reported as being effective. The 25 IU dose was not shown to be effective. 15 of the 40 subjects treated in study 6905 had a screening LH level below 1.2 IU/L. All subjects were evaluable except for subject 150002 in the 225 IU/day dose group, who had an elevated androstenedione level at screening. These 15 subjects were separated out by the sponsor and analyzed. In the evaluable patient analysis, no statistically significant effect of addition of r-hLH was demonstrated on the primary efficacy endpoint in the low LH subgroup (< 1.2 IU/L). Again, the best responses were seen in the 25 IU dose groups.

On July 10, 1998, the June 12, 1998 pre-NDA package was discussed with the applicant in a teleconference. The applicant was told that the U.S. study (6905) demonstrated no efficacy as did the “Low LH” subgroup analysis of the U.S. study. The applicant stated that the European study (6253) had demonstrated that the appropriate dose was 75 IU. The applicant was asked to submit intent-to-treat analyses for both the U.S. and the European studies.

On July 27, 1998, the applicant submitted an addendum to the pre-NDA package which included four different analyses:

1. An ITT analysis of study 6253 (European study)
2. An ITT analysis of study 6905 (U.S. study)
3. An ITT analysis of “low LH” subjects in study 6905
4. An ITT analysis which integrated subjects from study 6253 and the “low LH” subgroups from study 6905.

Analyses of "low LH" subjects in study 6905 and integrated subjects from study 6253 and the "low LH" subgroup from study 6905 had not been proposed or planned before completion of both studies. These two post-hoc analyses are referred to as "supportive analyses".

The purpose of the addendum was to confirm that the data derived from studies 6905 and 6253 were adequate for filing the NDA and for the approval of r-hLH for the proposed indication.

The results of the ITT analyses are:

- 1) A statistically significant dose-related trend was observed in the ITT analysis of study 6253.
- 2) The results of the analysis of follicular development for the ITT population of study 6905 were not statistically significant.
- 3) A statistically significant trend was observed in the ITT analysis of the primary efficacy endpoint for the 15 "low LH" patients in study 6905. (This was achieved by adding the one nonevaluable patient with follicular development who had an elevated androstenedione level at screening to the 225 IU dose group.)
- 4) A statistically significant dose-related trend was observed in the ITT analysis of the integrated "low LH" patients from studies 6253 and 6905.

On August 11, 1998, the July 27, 1998 addendum was discussed with the applicant in a teleconference. The following points were discussed:

- Studies 6253 (European) and 6905 (U.S.) were originally designed as dose finding studies with identical protocols and numbers of subjects
- Both studies are considered equally informative by the Division; because results were quite different in the two studies, another study is needed to demonstrate efficacy of the selected minimal effective dose
- There are other existing therapies for this condition currently available

- Greater than 50% of the patients in one study had follicular development with FSH alone and one patient became pregnant with FSH alone showing that LH is not needed for all patients
- A Gonal-F alone arm should be included in the pivotal study
- The sponsor was resistant to performing another study on the following basis:
 - it is too costly
 - it is too time-consuming
 - the two studies indicate efficacy of the 75 IU dose
- The Division suggested that another study could be performed in a reasonable time period based on the time needed for the previous studies
 - The European study was performed in 10 centers with 38 patients; it took 19 months to complete
 - The U.S. trial studied 43 patients in 15 centers and took 3 years to complete
 - There is an adequate patient base (145,000 patients per year) from which to obtain study subjects in the U.S.
- The data indicated that the most effective dose in the U.S. study was 25 IU when low LH patients are separated out; however the most effective dose in the European study was 75 and 225 IU in a pooled calculation
- Neither study showed a significant difference in efficacy at the projected endpoints; the most positive item reported was a dose-related trend in the ITT analysis of study 6253
- More data is needed before the NDA would be fileable
- Although both the U.S. study and the European study were designed as dose-finding studies, the studies made different dosing conclusions when the low LH patients were separated out

- The European study indicates that the dose should be started at 75 IU and titrated to 225 IU
- In the U.S. study (6905) 80% of subjects responded to the 25 IU dose when only low LH patients were evaluated
- Study 6905 showed the drug to be ineffective
 - In study 6905, the low LH patients who received the 25 IU dose showed the best response
 - The effect of the drug in the U.S. study may have been masked by the broader inclusion criteria used in recruitment that were recommended by the sponsor's investigators

The applicant responded September 4, 1998 with the submission of a summary of clinical information previously submitted in the pre-NDA meeting package and a restatement of their position that the data from studies 6905 and 6253 supported the filing approval of the NDA for the proposed orphan indication and the intended patient population. Quite noticeable was the fact that the applicant was now referring to study 6253 as the pivotal study and study 6905 as a supportive study.

On October 21, 1998 the fileability of the proposed NDA was discussed with the Director, Office of Drug Evaluation II and the Deputy Director, Center for Drug Evaluation and Research who agreed that if the NDA were submitted, it would not be fileable.

The applicant submitted a supplemental pre-NDA meeting package November 18, 1998 which contained new data from two additional clinical trials carried out in Europe. Study 7798 was conducted in Germany in a profoundly LH-deficient population (LH < 1.2 IU/L) while study 8297 was conducted in Spain in what the applicant stated was a moderately LH-deficient population (LH below or within normal range). These two new studies did not employ LH doses less than 75 IU. These studies were not designed to determine the minimal effective dose. In study 8297, 22 of 38 treated patients actually were "low LH" patients, but follicular development was the same in all patients as in "low LH patients". Study 7798 was a study of 15 subjects randomized to receive 75, 150, and 225 IU r-hLH, 5 subjects to each dose group for the first

treatment cycle and then crossed over to a higher or lower dose in subsequent cycles by a random scheme. For the first cycle of treatment, follicular development occurred in 60% of patients receiving 75 IU, 40% of patients receiving 150 IU, and 80% of patients receiving 225 IU.

The Deputy Director, ODE II and the Division staff met with the applicant November 30, 1998. The following points and decisions were discussed and reached:

- FDA Clinical Issues:
 - The sponsor is maintaining Orphan status for this indication
 - The sponsor now seeks to submit the European trial (6253) as the pivotal trial with three supportive studies from three different countries in support of an NDA; when the original protocols were submitted, neither the U.S. nor the European study was designated as pivotal; they were to be identical studies treated with equal weight
 - At the Pre-IND meeting held on May 21, 1992, the development plan was discussed; two studies, using the same protocol, were proposed, one in Europe and one in the USA
 - When the IND was submitted, only the protocol for the U.S. Study (6905) was included
 - In July 1994, a protocol amendment was submitted with significant changes in the U.S. protocol prior to initiation of the study
 - The European study is significantly different from the U.S. study
 - On November 18, 1998, new data from the Spanish study was submitted using moderately LH deficient patients
 - 15 patients were studied in a German study; there were six pregnancies in the 75 IU group, one in the 150 IU group, and none in the 225 IU dose group

- If efficacy is dose related, the fewer number of pregnancies in the higher dose group should be explained
- FDA Statistical Issues
 - The trend test is proposed as a confirmatory statistical tool for efficacy assessment
 - Step-down doses were studied, beginning with the highest dose, to show significance in order to avoid multiple-comparison doses and head-to head comparisons at lower alpha levels
 - FDA considers these trend tests to be exploratory tests and not significant for a pivotal trial
 - The U.S. and European studies were designed as dose-finding studies and no hypothesis was set for the studies at the outset; additionally, exploratory analyses were used to detect significance
 - This data can be used to make exploratory conclusions for further research; however, making efficacy conclusions based on these analyses is problematic
 - The analysis was a post-hoc comparison; no NDA has been approved using only one study analyzed using a trend test
 - These studies were not powered on any criteria other than the limited size of the patient population
 - The best overall result in the U.S. study was with the 25 IU, both in the overall study and the “low LH” subset

Sponsor's Points

- The 75 IU dose was chosen as the optimal dose
- The U.S. study protocol was changed because of enrollment problems

Decisions reached:

- Review issues will be discussed at the Office level

- The sponsor should submit a justification for the trend test analysis
- If filed, the application may be taken to an Advisory Committee
- A justification for the analyses can be sent after the fileability issue has been resolved
- The sponsor should clarify which studies will be used to support the NDA submission; any future approaches and plans should be submitted
- The German and Spanish study data should be submitted for review; the data will be available in April 1999
- The sponsor plans to submit the NDA in April 1999

The sponsor responded December 16, 1998 clarifying that they intended to rely on studies 6253 (Europe and Israel) and 7798 (Germany) as the basis for approval of their NDA.

A teleconference was held with the sponsor February 23, 1999 to discuss the fileability of this application. The following items were discussed and the following decisions made:

FDA Issues:

- The lowest effective dose for this product has not been clearly established
- The patient population who might benefit from Luveris™ has not been adequately defined; a broader patient population could be studied, for example, patients with LH levels < 5 IU/L
- The European study (Protocol 6253) included patients with LH levels < 1.2 IU/L; the 75 IU dose was determined by the sponsor to be the lowest effective dose in this study based upon 7 patients out of 11 patients who had follicular development vs. 1 out of 9 placebo patients who had follicular development

- The use of historical controls with the German study may not be adequate to show efficacy because:
 - The German study has many dropouts from later cycles of the cross-over study
 - Only 15 patients across 12 centers were enrolled
 - Not enough efficacy data has been gathered to distinguish the minimal effective dose
- A Phase 3 trial comparing the 75 IU dose to placebo should be performed; patients with LH levels < 5 IU/L could be enrolled; a significant subset of patients with LH levels < 1.2 IU/L should also be included
- All patients who are enrolled in the study should desire pregnancy as an outcome
- The primary clinical endpoint should be ovulation rates with pregnancy rates as a secondary outcome; a single cycle would be adequate to demonstrate efficacy regarding ovulation rate; after studying a one-month cycle, patients could be followed for pregnancy rates
- If the data show a benefit in patients with LH levels < 1.2 IU/L, the FDA would consider NDA approval for the limited population of patients with very low LH levels

Decisions:

- A new study should be performed which includes a wider inclusion criteria, with a more relevant patient population who would typically be considered for treatment with Luveris™
- The product labeling would include information that the product is not effective in patients with LH levels > 1.2 IU/L if the data from patients with LH levels > 1.2 IU/L show a lack of efficacy
- The current data base includes efficacy data from a placebo-controlled trial involving 11 patients who received 75 IU Luveris™ vs. 9 patients who received placebo; this is an

insufficient database for filing an NDA and would necessitate the initiation of the refusal-to-file procedure, should it be submitted

- If a study comparing the 75 IU dose of LH with historical control data is planned, the proposal should be submitted for comment; controls, sample size calculations, the primary endpoints and the definition of success should be included in the proposal
- The sponsor will consider these comments internally and convey a decision to the Division regarding performing an additional clinical study

The sponsor submitted a protocol for the additional clinical study March 22, 1999. A teleconference with the sponsor was held May 3, 1999 to convey comments to the sponsor regarding the trial design for this study (Protocol IMP 21008). The following points were discussed and the following decisions reached:

FDA Points:

- The sponsor wishes to study a population with LH level < 1.2 IU/L; although the Division prefers that the study population include patients with higher LH levels, it was agreed that the study could proceed, but the sponsor was reminded that the label would reflect negative results from patients with levels of LH < 5.0 IU/L but > 1.2 IU/L
- Single-dose study of 75 IU can be conducted with the caveat that the NDA application will be carefully reviewed regarding all dosage levels; safety of 25 IU vs. 75 IU doses in the patient population will be compared, and if the 25 IU is effective it could lead to a possible review issue given that the lowest effective dose was not studied
- The use of a placebo arm consisting of nine additional subjects with concurrent data, not historical data is recommended; this would be considered the pivotal study
- Both the ultrasonographer and patient should be blinded
- Since the primary endpoint is a combination of follicular development and mid-luteal progesterone levels, a more stringent cut-off of 10ng/mL for progesterone level should be considered as

a better indicator of follicular development instead of the proposed 7.8 ng/mL cut-off

- The 200 pg/mL is a more acceptable E₂ level as an indicator of follicular development than the proposed 109 pg/mL E₂ level

Decisions reached:

- Sponsor will attempt to blind the study as much as possible and re-submit the protocol
- The E₂ and progesterone levels will be reevaluated and a valid argument for the proposed levels will be submitted for review
- The estimated success rate should be recalculated for each treatment group using the new criteria since the P₄ level (and possible E₂ level) used to determine the treatment success may change
- The sample size for the pivotal study reflecting the revised estimates of anticipated success rates and the addition of a placebo arm should also be recalculated

Post-meeting Addendum:

- A phone call was made to the sponsor requesting them to submit a justification or rationale as to why blinding is so difficult for this study in the revised protocol

II Clinically Relevant Findings from Chemistry, Toxicology, and Microbiology:

Please refer to the chemist's, pharmacologist's, and microbiologist's reviews for pertinent findings.

III Human Pharmacokinetics and Pharmacodynamics:

Recombinant-hLH shows linear pharmacokinetics after IV doses ranging from 75 IU to 40,000 IU, as assessed by the area under the curve. The AUCs are directly proportional to the dose administered; additionally, the clearance remains almost constant throughout the studies. Around 5% of the dose are excreted unchanged in the urine.

The terminal half-life of r-hLH administered SC is around half a day. This is best estimated when high doses are injected, as those obtained with much lower doses are less precise given the larger impact of fluctuations in baseline.

The absolute bioavailability was approximately 60% for both the IM and SC routes.

Recombinant hLH and urinary hLH have similar pharmacokinetics when assessed by immunoassay. The only exception was a lower fraction excreted unchanged in the urine following administration of r-hLH.

There is no pharmacokinetic interaction between r-hLH and r-hFSH. After repeated SC administration, the pharmacokinetics of r-hLH are comparable to those found after single SC administration.

When administered SC concomitantly at the dose of 150 IU per day, r-hLH does not markedly affect the response to r-hFSH.

In conclusion, r-hLH was well tolerated at all doses administered, whether given as single or repeated dose injections.

IV Description of Clinical Data and Sources:

- A. Overall data are from clinical trials.
- B. The sponsor completed five small clinical trials.

Two controlled dose-finding studies were conducted to evaluate doses of r-hLH ranging from sub-therapeutic to supra-therapeutic (Study 6253 and Study 6905) with FSH alone; two additional studies were designed to address efficacy and safety over a range of doses reflecting anticipated clinical usage (Study 7798 and Study 8297), and one study (Study 21008) evaluated one dose of r-hLH given concomitantly with FSH. Three of the studies targeted women with severe LH deficiency (studies 6253, 7798 and 21008) and two (Studies 6905 and 8297) addressed more moderate levels of gonadotropin deficiency. The primary clinical endpoint for all studies was follicular development as defined by three criteria: 1) follicle size, 2) pre-ovulatory serum estradiol levels and 3) mid-luteal progesterone levels, all of which had to be present.

The dose of 75 IU was chosen by the sponsor . Study 6253 evaluated doses of r-hLH of 0, 25, 75, and 225 IU. The results of Study 6253 identified a positive trend between dose of r-hLH and follicular development and 75 IU was identified as the effective dose by the sponsor and as an exploratory dose by FDA reviewers. Study 21008 was a double-blind, placebo-controlled, randomized trial to confirm the efficacy of the 75 IU r-hLH dose compared to placebo when co-administered with 150 IU r-hFSH daily. The results of Study 21008 do not support the efficacy and safety of co-administration of 75 IU r-hLH with r-hFSH to support follicular development, steroidogenesis and ovulation in women with severe LH and FSH deficiency. Two additional controlled studies were designed to address efficacy and safety of r-hLH over a similar range of doses 0, 25, 75, 150 and 225 IU in women with hypogonadotropic hypogonadism (Study 6905 and Study 7798) with more moderate levels of gonadotropin deficiency. A dose response to concomitant administration of r-hLH and r-FSH was not demonstrated in study 6905 which was the original pivotal study performed in the United States under IND 44,108. Studies 7798 and 8297 did not assign subjects to doses of r-hLH below 75 IU. Also, study 8297 did not include a control arm.

- C. Postmarketing experience is not available. The drug has been launched for marketing in nine countries during the past year, but the sponsor has not received any adverse event reports.

V Clinical Review Methods:

- A. The five small clinical trials were reviewed in detail.
- B. IND 44,108 was evaluated
- C. DSI audit of four investigators was satisfactory. Several protocol violations and record keeping inadequacies were noted, but these are not serious enough to adversely impact on the acceptability of generated study data.
- D. The informed consents and standard of patient care were satisfactory in the clinical studies reviewed.

VI Review of Efficacy:

- A. Findings in Light of Proposed Labeling claims

Human menopausal gonadotropins (urinary derived FSH and LH) have been used for many years for the treatment of H.H., but menotropins has never been evaluated for this indication by FDA. The optimal clinical study would be to compare directly in a head to head fashion the combination of r-hLH and r-hFSH with human menopausal gonadotropins. However, no approved menotropins has H.H. as an indication and the analysis would have to compare Luveris™ to menotropins historical data and there is a paucity of such historical data. The applicant did not accept this recommendation from FDA. The draft labeling fails to mention that no direct comparison has been performed.

While the draft labeling states that the drug is indicated for women with severe LH and FSH deficiency, it fails to define “severe” as being an endogenous serum LH level less than 1.2 IU/L and FSH level < 5.0 IU/L.

The original claim for this drug was for the treatment of all patients diagnosed as H.H. The original pivotal U.S. study (study 6905) failed to show efficacy in this patient population, but this information does not appear in the draft labeling.

Since the requested indication is “induction of ovulation”, the efficacy table should be “ovulation Rate” rather than “Follicular Development Rate”.

B. Integrated Summary of Efficacy:

The primary reason for treating patients with H.H. is the achievement of pregnancy for women who desire it. A total of 100 patients in 5 studies receiving 75 IU of r-hLH and r-hFSH sought pregnancy. There were 31 pregnancies (31%) in this group. Of 41 patients desiring pregnancy who received placebo (no r-hLH) and r-hFSH, 17% became pregnant.

The primary endpoint for the five studies was follicular development as defined by three criteria: 1) follicle size, 2) pre-ovulatory serum estradiol levels and 3) mid-luteal phase progesterone levels indicating ovulation. The efficacy results for study 21008 are summarized in Table 1 for evaluable patients, which are similar to the ITT population. This is now the pivotal study. These results include as successes subjects whose treatment was cancelled due to risk of developing OHSS.

Table 1(Sponsor's Table 13)Follicular Development Rate (Evaluable Patients, Study 21008)

Follicular Development	Placebo and r-hFSH n = 10 (%)	75 IU r-hLH and r-hFSH n = 24 (%)
Yes	2 (20.0)	16 (66.7)
No	8 (80.0)	8 (33.3)

The efficacy results for study 6253 are summarized in Table 2 for evaluable patients, which are similar to the ITT population. These results include as successes subjects whose treatment was cancelled due to risk of developing OHSS.

Table 2
(Sponsor's Table 5)

Follicular Development (Evaluable Patients, Study 6253)

Follicular Development	Placebo and r-hFSH N= 8 (%)	25 IU r-hLH and r-hFSH n = 7 (%)	75 IU r-hLH and r-hFSH n = 9 (%)
Yes	0 (0)	1 (14)	6 (67)
No	8 (100)	6 (86)	3 (33)

The efficacy results for study 6905 (the original pivotal U.S. study) are summarized in Table 3 for evaluable patients, which are similar to the ITT population. These results include as successes subjects whose treatment was cancelled due to risk of developing OHSS. A dose of 25 IU is at least as effective as 75 IU.

Table 3
(Sponsor's Volume 80)

Follicular Development Rate (Evaluable Patients, Study 6905)

Follicular Development	Placebo and r-hFSH n = 11 (%)	25 IU r-hLH and r-hFSH n = 9 (%)	75 IU r-hLH and r-hFSH n = 11 (%)
Yes	7 (64)	9 (100)	8 (73)
No	4 (36)	0 (0)	3 (27)

The efficacy results for study 6905 for the subset of patients with serum LH levels less than 1.2 IU/L are summarized in Table 4 for evaluable patients, which are similar to ITT population. These results include as successes subjects whose treatment was cancelled due to risk of developing OHSS. Again, a dose of 25 IU of Luveris™ is shown to be at least as effective as 75 IU of Luveris™.

Table 4
(Sponsor's Table 2)

Follicular Development Rate (Evaluable Patients, Study 6905, LH < 1.2 IU/L Subset)

Follicular Development	Placebo and r-FSH n = 3 (%)	25 IU r-hLH and r-hFSH n = 5 (%)	75 IU r-hLH and r-hFSH n = 3 (%)
Yes	0 (%)	5 (100)	2 (67)
No	3 (100)	0 (0)	1 (33)

Study 7798 was a dose finding study of 75, 150, and 225 IU/day. A total of 15 patients were treated in cycle 1. Only 2 of 5 (40%) in the 75 IU/day group, 1 of 5 (20%) in the 150 IU/day group, and 3 of 5 (60%) in the 225 IU/day group met the criteria for successful follicular development.

Study 8297 has no relevance for the presently proposed indication because eligible patients included women with normal serum gonadotropin levels and the study was an open-label, non-comparative, single-arm study.

A different efficacy picture is seen when ITT analyses are performed and subjects whose treatment was cancelled due to risk of developing OHSS are considered as failures. The efficacy results for study 21008 are summarized in Table 5 showing that Luveris™ may not be different from placebo.

Table 5

(FDA Statistician's Table 4)

Follicular Development Rate (ITT Patients, Study 21008)

Follicular Development	Placebo and r-hFSH N = 13 (%)	75 IU r-hLH and r-hFSH n = 26 (%)
Yes	1 (8.0%)	10 (38.0%)
No	12 (92.0%)	16 (62.0%)

The efficacy results for study 6253 are summarized in Table 6 showing, again, that Luveris™ may not be different from placebo.

Table 6

(FDA Statistician's Table 7)

Follicular Development Rate (ITT) Patients, Study 6253)

Follicular Development	Placebo and r-hFSH n = 9 (%)	25 IU r-hLH and r-hFSH n = 8 (%)	75 IU r-hLH and r-hFSH n = 11(%)
Yes	1 (11%)	2 (25%)	5 (45%)
No	8 (89%)	6 (75%)	6 (55%)

In study 21008, when considering subjects with cancelled cycles because of the risk of OHSS as failures, follicular development occurred in 38% of subjects receiving 75 IU r-hLH and in 8% of subjects receiving only r-hFSH. In study 6253, when considering subjects with cancelled cycles because of the risk of OHSS as failures, follicular development occurred in 45% of subjects receiving 75 IU r-hLH, 25% of subjects receiving 25 IU r-hLH, and 11% of subjects receiving only r-hFSH.

VII Integrated Review of Safety:

The safety of Luveris™ was determined in the five clinical trials in which 142 patients received Luveris™ and r-hFSH. For all patients treated with any dose of Luveris™ and r-hFSH, adverse events reported in 2 or more patients (regardless of causality) are shown in Table 7. A total of 63 patients (44.4%) experienced at least one adverse event.

Table 7
Incidence of Adverse Events in Five Studies Totaling 142 Patients

<u>Adverse Event</u>	<u>n (%)</u>
Headache	14 (9.9)
Abdominal Pain	12 (8.5)
Nausea	9 (6.3)
Ovarian hyperstimulation syndrome	8 (5.6)
Breast pain	7 (4.9)
Ovarian cyst	7 (4.9)
Injection site reaction	6 (4.2)
Pelvic pain	5 (3.5)
Dysmenorrhea	4 (2.8)
Fatigue	4 (2.8)

A total of 21.7% of 92 patients receiving 75 IU of Luveris and 11.8% of 17 patients receiving 25 IU of Luveris™ had their treatment cycle cancelled because of the risk of ovarian hyperstimulation.

VIII Assessment of Dosing Issues:

The pivotal study (study 21008) revealed that 16 of 24 patients receiving 75 IU of Luveris™ (66.7%) experienced follicular development while 2 of 10 patients receiving placebo (20%) did so. This finding is similar to the results seen in study 6253 where 67% of patients treated with 75 IU of Luveris™ (6 of 9 patients)

experienced follicular development while 0 of 8 patients receiving placebo and 1 of 7 patients (14%) receiving 25 IU of Luveris™ did do. This finding is also similar to the results seen in the LH < 1.2 IU/L subset of study 6905 where 67% (2 of 3) of patients receiving 25 IU of Luveris™ experienced follicular development. However, in this subset, 100% (5 of 5) of patients receiving 25 IU of Luveris™ experienced follicular development which casts doubt on the need for 75 IU of Luveris™.

This finding is also similar to the results seen in study 6905 where 73% (8 of 11) of patients receiving 75 IU of Luveris™ experienced follicular development while 100% (9 of 9) of patients receiving 25 IU of Luveris™ experienced follicular development. Clearly, the minimal effective dose of Luveris™ for this indication may not be 75 IU. This is relevant in that 21.7% (20 of 92) of all patients across all populations receiving 75 IU of Luveris™ had their treatment cycle cancelled because of the risk of ovarian hyperstimulation while only 11.8% (2 of 17) of all patients receiving 25 IU of Luveris™ had their treatment cycle cancelled because of the risk of ovarian hyperstimulation.

IX Use in Special Populations:

- A. Treatment for ovulation induction is applicable only for females.
- B. This treatment is not indicated for pediatric patients.
- C. It is not anticipated that race or ethnicity would make a difference in the effect of the drug. Most of the patients studied were Caucasian. In study 6905, 77.5% of the patients were Caucasian. In study 6253, all patients were Caucasian except for one Asian. In study 21008, 79.5% of the patients were Caucasian, 12.8% were Hispanic, 2.6% were Black, and 5.1% were of "other" race.
- D. Clinical studies did not include elderly patients. The safety and efficacy of the drug in renal and hepatic insufficiency have not been studied. The drug is contraindicated in pregnancy.

X Conclusions and Recommendations:

A. Overall Risk-Benefit Analysis:

The benefit to risk relationship of Luveris™ is uncertain. The benefits of the drug may not outweigh its risks. The safety profile of Luveris™ is acceptable, but the efficacy profile of the drug has not been established.

LH supplementation of FSH is a long-established therapeutic modality in the treatment of H.H. Menotropins has been used for this purpose "off label", but menotropins were never evaluated by FDA for this indication. It is not known how effective menotropins are. Given the long history of use and safety in clinical practice of menotropins, Luveris™ with r-hFSH may have a similar clinical profile as menotropins.

Overall, it is difficult to determine if this drug has any or much benefit for this indication. The only sure thing is that the original U.S. study (study 6905), conducted in a traditional population of H.H. as determined by the sponsor's expert clinical investigators, yielded results that indicated that Luveris™ is ineffective for treatment of H.H.

While it is known that menotropins (combination of FSH and LH) have been used, off label, for the treatment of H.H. for many years, there is no good data to show how effective it is. Considerable variation exists in the endocrine profile of H.H. There is some overlap in hormone levels between H.H. subjects and normal women, and randomly obtained serum gonadotropin levels may be low or normal. It is known that some H.H. patients respond to FSH alone. Shoham, in 1991, compared treatment of profoundly deficit H.H. patients using menotropins in one cycle of treatment, and FSH alone in the next cycle of treatment. All patients had screening LH of ≤ 1.2 IU/L. When menotropins was given, all 9 patients ovulated as determined by luteal phase serum progesterone levels. When FSH alone was administered, three of the subjects ovulated, indicating that LH was not required. There was nothing in the screening endocrine characteristics of those responding to FSH alone that differentiated them from non-responders or that would have predicted a response. Clearly, some profoundly LH-deficient patients respond to FSH alone. This unpredictable response to FSH alone is due to FSH-stimulated paracrine factors that induce LH-like effects on the theca cell. Ideally, the Agency would also like to see a direct head-to-head comparison of r-hLH/r-hFSH versus menotropins. This recommendation by FDA to the sponsor was not implemented.

In women undergoing gonadotropin therapy, an excessive response to follicular stimulation may lead to the development of OHSS, a life-threatening condition, particularly if hCG is given to induce ovulation. Subjects in these studies were considered to be at risk of developing OHSS if serum estradiol concentrations increased rapidly and/or there was an excessive number of growing follicles visualized. In such cycles, hCG was to be withheld and the cycle cancelled. Risk of OHSS is a safety-

related event and was to be recorded as such. In study 6905 trend analyses were performed with and without overstimulation counted as a success. In study 21008, overstimulation resulting in cancellation of the cycle was considered as a success. The conundrum is whether cancelled cycles due to overstimulation should be counted as successes or failures. Obviously, from a clinical point of view, for the treating physician and the patient, they are failures. From the sponsor's view point, they may be thought of as successes in that the pharmacological action of the drug resulted in follicular development and hCG was not given to trigger ovulation only because it was unsafe.

However, cycle cancellation due to risk of OHSS is not a benefit for the patient and not a success for the patient. The sponsor acknowledged this in their supplemental pre-meeting package dated November 18, 1998. In the discussion of the ITT analysis of study 6253, the sponsor stated that follicular development occurred in 70.0% of patients receiving 225 IU OF Luveris™ and in 63.6% of patients receiving 75 IU of Luveris™. However, the 6.4% increased response seen in the 225 IU group (70.0% versus 63.6% in 75 IU) was associated with a greater likelihood of cycle cancellation due to risk of OHSS. For the 6.4% gain in efficacy at this higher dose, there was an approximately 12% increase in cycle cancellation due to risk of hyperstimulation. For this reason, 225 IU was not chosen as the appropriate dose and 75 IU was chosen.

In study 21008 there was a 27% gain in efficacy claimed by counting 23% of patients with cancelled cycles as successes. It was for this reason that the sponsor was informed in a teleconference February 23, 1999 that a decision had been made that the primary clinical endpoint should be ovulation rates with pregnancy rates as a secondary outcome. Ovulation would be determined on the basis of midluteal phase serum progesterone levels. On this basis, success occurred in only 46% of patients receiving 75 IU of Luveris™. If the patients with cancelled cycles receiving 75 IU of Luveris™ had been given 25 IU or 50 IU of Luveris™ and ovarian hyperstimulation had not occurred, a much larger percentage of patients would have benefited by successful ovulation. On the basis of all currently available data, one cannot determine that the benefit to risk ratio for this drug is favorable. Ovulation occurred in 45% of patients receiving 75 IU of Luveris™ in study 6253.

B. Remaining Unresolved Issues:

Determination of lowest effective dose. Efficacy of Luveris™ for this indication.

C. Major Needed Changes Regarding Draft Package Insert:

In the “Indications section”, “severe LH and FSH deficiency” needs to be defined as being an endogenous serum LH level less than 1.2 IU/L and an endogenous FSH level less than 5.0 IU/L.

Table 4 and relevant narration regarding adverse events are superfluous and should be deleted.

D. Approval of this application is not recommended. The minimal effective dose has not been clearly established. There is not sufficient evidence to show that Luveris™ treatment is clinically or statistically significantly different from that of placebo.

E. Post-Marketing Risk Management Studies Recommended:

If this drug product is approved, I would recommend followup of children born to all treated study patients should occur and be reported to FDA.

XI. Individual Study Reviews

Study 6253 began in September, 1993.

Study Title

“An open label, randomized, dose-finding, multicenter, pivotal study to determine the minimal effective dose and to assess the safety of recombinant human Luteinizing Hormone (r-hLH) to support recombinant human Follicle Stimulating Hormone (r-hFSH induced follicular development in LH and FSH deficient anovulatory women (WHO Group I).”

Investigator/Location

The study was conducted in 10 centers in Europe and Israel.

Study Objectives

- To assess the need for an efficacy of r-hLH for inducing ovulation in WHO Group I anovulation.
- To determine the minimal effective dose of r-hLH to be administered during r-hFSH stimulation of follicular development.
- To assess the safety of r-hLH administered subcutaneously to women for up to 20 days at a dose of up to 225IU/day.

Study Design

This study was designed as a Phase II/III, multicenter, open label, randomized comparative, parallel group, dose finding study to determine the minimal effective dose and assess the safety of r-hLH to support the r-hFSH induced follicular development in LH and FSH deficient anovulatory women (WHO Group I). Thirty-two women were planned to be included in the study (8 per group). Patients with a previous relevant history of severe OHSS were excluded from study.

Eligible patients were to be allocated to a treatment group receiving 0, 25, 75 or 225 IU of r-hLH daily SC according to a computer generated randomization list. A fixed dose of 150 IU r-hFSH was to be administered SC every day at approximately the same time as the rhLH. The administration of r-hLH and r-FSH was not to exceed 14 days in any cycle unless E₂ rose and/or follicular growth was observed. If this was the case, patients could continue the treatment up to a maximum of 20 days. Follicular growth was monitored by ultrasound and serum E₂ levels. Each patient was allowed to participate in up to three treatment cycles (A, B, and C) depending on her response to the first and second cycles. However, Cycles B and C were optional; in these cycles, the r-hLH dose was decided based on the response to the previous cycles.

Patient Population

A minimum of 32 female patients with primary or secondary hypogonadotropic hypogonadism who were either volunteers or wishing to conceive, were to be included in the study. They were to be between the ages 18-35 years with a negative progesterone challenge test, serum LH less than 1.2 IU/L, an ultrasound showing a uterus with a midline echo, no ovarian tumor or cyst and less than or equal to 13 (vaginal probe) or 10 (abdominal probe) small follicles on the largest section through each ovary. Patients were also required to have a BMI between 18.4 and 31.4

kg/m², no systemic diseases, and use mechanical contraception if not wishing to conceive.

Patient Disposition

Thirty-eight patients were randomized, entered into the clinical phase of the protocol and treated for up to 3 cycles for a total of 53 cycles (39 Cycle A, 9 Cycle B and 5 Cycle C).

Safety Results

A total of 42 AEs were reported in 14 (26.4%) of the 53 cycles. Thirty-two of these AEs occurred in 11 (26.2%) of the 42 cycles treated with r-hLH, and 10 occurred in 3 (27.2%) of the 11 cycles not treated with r-hLH. The most frequently occurring events were headache, pelvic and abdominal pain, breast pain, nausea, somnolence and ovarian disorder. Two serious AEs occurred: one patient was involved in a car accident and another suffered a miscarriage.

Efficacy Results

During Cycle A, 27 patients received hCG, 5 did not receive hCG because of risk of OHSS, 14 did not receive hCG because of insufficient follicular development and 2 withdrew consent. In the 0 IU and 25 IU LH dose groups, a minority of patients had good or excessive follicular growth (6/17) contrasting with the 75 IU and 225 IU LH dose groups in which a majority of patients had good or excessive follicular growth (15/21). The proportion of patients who fulfilled the primary efficacy endpoint criteria was related to the dose of r-hLH (11.1%, 25.0%, 63.6%, and 70.0% for treatment with 0, 25, 75 and 225 IU r-hLH respectively; p=0.0044).

Study 6905 was begun in July, 1994.

Study Title

“An open, randomized, dose finding, multicenter study to determine the minimal effective dose and to assess the safety of r-hLH to support r-hFSH induced follicular development in anovulatory women with hypogonadotropic hypogonadism.”

Investigator/Location

The study was conducted in 14 centers in the United States.

Study Purpose

The study objectives were:

- To assess the need for and efficacy of r-hLH for inducing ovulation in women with hypogonadotropic hypogonadism.
- To determine the minimal effective dose of r-hLH to be administered during r-hFSH stimulation of follicular development.
- To assess the safety of r-hLH administered SC to women for up to 21 days per cycle for a maximum of three cycles at a dose of up to 225 IU/day.

Study Design

The study was designed as an open, randomized, dose finding, parallel group, multicenter study to determine the minimal effective dose and the efficacy and safety of r-hLH. Recombinant LH was administered SC at doses up to 225 IU/day to support stimulation of follicular development with a fixed dose of 150 IU/day of r-hFSH in anovulatory women with hypogonadotropic hypogonadism. Patients with a previous history of moderate or severe OHSS were excluded from study.

Once patient eligibility had been established and the patient was ready to start the study, she was to be allocated to treatment with one of the four r-hLH dosages: 0, 25, 75 or 225 IU/day, according to a computer generated randomization sequence. After a negative pregnancy test, qualified patients were to start daily r-hLH and r-hFSH injections. Recombinant-hLH at the randomized dose and r-hFSH, at the fixed dose of 150 IU were to be administered daily at the same time between 7:00 and 10:00 PM, both subcutaneously. The primary endpoint chosen for the study was follicular development as defined by at least one follicle with a mean diameter of greater than or equal to 17mm and pre-ovulatory serum E₂ level \geq 160 pg/ml and lastly, a mid luteal phase P₄ level of \geq 10 ng/mL.

Patient Population

Thirty-two premenopausal anovulatory women with hypogonadotropic hypogonadism between the ages of 18 and 40 years were to be enrolled.

They were to have had serum values of $\text{LH} \leq 13.3$ IU/L, $\text{FSH} \leq 10.85$, an ultrasound showing a normal uterus, no ovarian tumor or cyst and less than or equal to 13 follicles on the largest section through each ovary; BMI between 18 and 35 kg/m^2 , without systemic disease.

Patient Disposition

Forty-three patients were randomized of whom 40 received study drug and were treated for up to 3 cycles for a total of 61 cycles (40 Cycle A, 16 Cycle B and 5 Cycle C). As planned, the primary efficacy analysis was conducted on the results of cycle A, the randomized cycle, and included all 40 patients; 11 patients in the 0 IU/day dose group; 9 in the 25 IU/day dose group; 11 in the 75 IU/day group; and 9 in the 225 IU/day group.

Safety

Over the entire course of the study, a total of 91 adverse events were reported. The most commonly reported events included ovarian cyst, abdominal pain, breast pain, dysmenorrhea, headache and nausea. No serious adverse events were reported during the study and none of the patients discontinued the study due to adverse events.

Efficacy

In Cycle A, the follicular development rate was lower in the 0 IU/day dose group, with 63.6% of the 11 patients meeting the criteria for follicular development. All 9 patients in the 25 IU/day dose group, 8 (72.7%) of 11 patients in the 75 IU/day dose group and 6 (66.7%) of 9 patients in the 225 IU/day dose group achieved follicular development.

To assess the efficacy of r-hLH in a US population similar to that studied in a similar study conducted by Serono in Europe and Israel (Study 6253), a subset analysis was performed on the primary efficacy endpoint for those 15 patients with a more profound endocrine secretory defect (pre-study $\text{LH} < 1.2$ IU/L). A statistically significant dose related benefit was observed ($p=0.039$) when the 0 IU dose was compared to the combined 75 IU and 225 IU dose groups.

Study 7798 began in September, 1995

Study Title

“A phase III multicenter study for the evaluation of the efficacy and safety of recombinant human Luteinizing Hormone (r-hLH) to support recombinant human Follicle Stimulating Hormone (r-hFSH)-induced follicular development in LH and FSH deficient anovulatory women (WHO group I).”

Investigator/Location

A total of 7 centers in Germany participated in the trial.

Study Purpose

The objectives of this study were:

- To assess the need for and efficacy of r-hLH in WHO Group I anovulatory women to support follicular development and induce ovulation.
- To evaluate the safety of r-hLH administered subcutaneously.

Study Design

This was an open, randomized, dose finding, crossover, multicenter study to determine the efficacy and safety of r-hLH, administered SC at doses of 75, 150 and 225 IU/day to support stimulation of follicular development with a fixed dose of 150 IU/day of r-hFSH in anovulatory women with hypogonadotropic hypogonadism, whose endogenous serum LH was < 1.2 IU/L.

Once a patient's eligibility was established and she was ready to start the study, the patient was to be randomized to treatment with one of six r-hLH dosage sequences of three dose levels over the 3 treatment cycles. Patient treatment assignment was determined by the following computer-generated randomization sequence:

Sequence	r-hLH Dose (IU/.day):		
	Cycle 1	Cycle 2	Cycle 3
A	75	150	225
B	75	225	150
C	150	225	75
D	150	75	225
E	225	150	75
F	225	75	150

The primary endpoint was follicular development as defined by at least one follicle with a mean diameter of ≥ 17 mm, pre-ovulatory serum E_2 level ≥ 200 pg/mL on the day of hCG administration, and a mid luteal phase P_4 level of > 10 ng/mL.

Patient Population

Twenty premenopausal women, aged 18-39 years, willing to conceive, with a clinical history of hypogonadotropic hypogonadism including low serum values of FSH (< 5 mIU/mL), LH (< 1.2 mIU/mL), estradiol ($E_2 < 50$ pg/mL), thyroid stimulating hormone (TSH < 6.5 uIU/mL), testosterone (T < 1.0 ng/mL) and prolactin (PRL < 32 ng/mL); an ultrasound showing endometrial thickness of less than or equal to 5 mm, no ovarian tumor or cyst and less than or equal to 10 small follicles on the largest section through each ovary; BMI between 15 and 31.4 kg/m² and having signed informed consent. The patient must have stopped treatment with pulsatile GnRH, gonadotropins or estrogen/progesterone replacement therapy at least one month prior to screening and have had a negative progesterone challenge test or no adult reaction after a GnRH test.

Patient Disposition

A total of 15 patients were treated in Cycle 1, 11 continued in Cycle 2 and 7 were treated in Cycle 3, for a total of 33 treatment cycles. Overall, 12 patients received 75 IU/day dose of r-hLH, 11 patients the 150 IU/day dose and 10 received the 225 IU/day dose. Eight patients withdrew prematurely from the study, 2 while being treated with 75 IU/day, 5 while being treated with 150 IU/day and 1 while being treated with 225 IU/day. Reasons for withdrawal prior to the third cycle were: 3 for pregnancy, 2 for OHSS or risk of OHSS, 2 for other reasons (non-compliance, spontaneous pregnancy during a rest cycle) and 1 for administrative reasons (personal decision).

Safety

Subcutaneous injections of up to 225 IU/day r-hLH in combination with Gonal-F® were safe and well tolerated. Four (26.7%) of the 15 patients treated in this study experienced at least one adverse event. All but one incident were reported during Cycle 1. During Cycle 1, two patients receiving 225 IU/day dose of r-hLH reported adverse events as did 1 patient receiving 150 IU/day and 1 receiving 75 IU/day. Only one patient receiving 75 IU/day reported adverse events during Cycle 2. The most

commonly reported adverse event was OHSS; 4 occurrences of OHSS were reported in 3 patients, 2 with 75 IU and 1 each with 150 IU and 225 IU. These incidents were of moderate to severe intensity. Four serious AEs, all OHSS, were reported in 3 patients during the study; all required hospitalization. Two patients were discontinued from the study because of OHSS.

Efficacy

By completion of Cycle 1, 6/15 (40%) met the criteria for successful follicular development, 2/5 (40%) in the 75 IU/day group, 1/5 (20%) in the 150 IU/day group and 3/5 (60%) in 225 IU/day group. Over the entire study, 17 patient cycles met the criteria for successful follicular development. At the completion of the study, the rate of successful follicular development was 58.3% for the 75 IU/day dose, 36.4% for the 150 IU/day dose and 60% for the highest dose at 225 IU/day. The lowest rate of successful development was during Cycle 1 (40%), with the success rates for Cycles 2 and 3 being similar (63.3% and 57.1%, respectively).

Study 8297 was begun in March, 1996

Study Title

“A phase III multicenter, non-comparative study to evaluate the efficacy and safety of recombinant Luteinizing Hormone (r-hLH) to support recombinant human Follicle Stimulating Hormone (r-hFSH)-induced follicular development in LH and FSH deficient anovulatory women (WHO Group I).”

Investigator/Location

A total of 14 centers in Spain participated in this clinical trial.

Study Purpose

The objectives of this study were:

- To assess the efficacy of r-hLH associated with r-hFSH in WHO Group I anovulatory women to support follicular development and induce ovulation.

- To evaluate the safety of r-hLH administered subcutaneously.

Study Design

Study 8297 was designed as an open-label, non-comparative, multicenter trial that enrolled LH and FSH deficient anovulatory WHO Group I women to assess the need for and efficacy of r-hLH to support recombinant human Follicle Stimulating Hormone (r-hFSH)-induced follicular development. Once patient eligibility had been established and after a negative pregnancy test was confirmed, qualified patients were to start daily r-hLH and r-hFSH injections. A fixed daily dose of 150 IU of r-hFSH was used. In cycle 1, patients received 75 IU r-hLH. However, if the patient had no follicular development, the patient could be treated with 150 IU r-hLH in the second cycle and 225 IU r-hLH in the third cycle. Unlike Studies 21008, 6253, and 7798 where the pre-study FSH had to be < 5 IU/L and LH levels had to be below 1.2 IU/L, the pre-study FSH and LH levels in this study could be below or within the normal ranges.

Duration of treatment with r-hLH and r-hFSH was not to exceed 21 days in any cycle and patients could be treated for a maximum of 3 cycles. Primary efficacy endpoint was follicular development as defined by at least one follicle with a mean diameter of greater than or equal to 18 mm and a mid luteal phase P_4 level of greater than or equal to 30 nmol/L.

Patient Population

Eligible patients were premenopausal women with hypogonadotropic hypogonadism, aged 18-35 years with low or normal serum gonadotropin values and a negative progesterone challenge test; an ultrasound showing a normal uterus, no ovarian tumor or cyst and less than or equal to 13 follicles on the largest section through each ovary; BMI between 18.4 and 31.4 kg/m², no systemic disease, no previous relevant history of severe OHSS and having signed informed consent.

Patient Disposition

Thirty-eight patients received study drug for up to 3 cycles for a total of 85 treatment cycles (38 Cycle A, 29 Cycle B and 18 Cycle C).

Efficacy

In Cycle 1, 26 of 38 patients (68.4%) received hCG to induce final follicular maturation and ovulation. Twenty-two out of 26 patients given hCG (84.6%) showed evidence of adequate luteinization and ovulation while the other four patients had missing serum P₄ levels, so this could not be assessed. The follicular development results obtained in Cycles B and C were comparable to those obtained in Cycle A. Considering all the cycles (A, B, and C), hCG was administered in 64 (75.3%) out of 85 initiated cycles and 81.2% of the cycles where hCG was given showed evidence of ovulation.

Safety

Over the entire course of this study, a total of 10 adverse events not related to injection site reactions were reported in 9 patients. The most commonly reported adverse event was OHSS, which occurred in 3 patients, all with 75 IU of Luveris™. Five serious adverse events were reported: two OHSS events in two patients; one miscarriage; and 2 inguinal hernias, one in each newborn twin of one patient. The 2 OHSS events were reported as moderate cases that required hospitalization; both patients (Patients 301 and 1201) were pregnant and both had been treated with 75 IU r-hLH. Each continued her pregnancy and successfully delivered a singleton. Patient 005-0003 (who had been treated with 75 IU r-hLH) delivered twins, each of whom had inguinal hernias and underwent corrective surgery. Patient 011-0003 had a miscarriage at 23 weeks gestation. The SAEs that occurred during the pregnancies of Patient 005-0003 and Patient 011-0003 were not reported at the times of the events and thus were not provided as events in the study report. Local tolerance at the injection demonstrated more than 90% of the injections having no itching, redness, swelling, bruising or pain reported.

Study 21008 began in February, 2000.

Study Title

“A phase III, prospective, randomized, controlled, double-blind, multicenter study to confirm the efficacy and safety of recombinant human Luteinizing Hormone (r-hLH), 75 IU, administered subcutaneously, to support recombinant human Follicle Stimulating Hormone (r-hFSH)-induced follicular development in women with hypogonadotropic hypogonadism and severe LH deficiency who desire pregnancy.”

Investigator/Location

This study was conducted at 25 centers throughout the US, Canada, Israel and Australia.

Study Objective

The study was designed to confirm the efficacy and safety of the 75 IU dose of r-hLH co-administered with 150 IU r-hFSH for induction of follicular development in women with hypogonadotropic hypogonadism (H.H.) and profound LH deficiency ($LH < 1.2$ IU/L) who desired pregnancy.

Study Design

This was a prospective, randomized, double-blind, placebo-controlled study. Patients were randomized in a 2:1 design to receive either r-hLH 75 IU and 150 IU r-hFSH, or placebo and 150 IU r-FSH.

The primary efficacy endpoint was achievement of adequate follicular development as defined by three conditions:

- 1) At least one follicle ≥ 17 mm
- 2) Serum estradiol (E_2) level ≥ 109 pg/mL (400 pmol/L) on the day of hCG.
- 3) Mid-luteal phase progesterone (P_4) level ≥ 7.9 ng/mL (25 nmol/L).

Patients terminated for risk of OHSS or patients achieving pregnancy were counted as successes for follicular development. Additional endpoints to assess efficacy included follicle size and number on the day of hCG, serum E_2 level across treatment, endometrial growth, and evidence of ovulation as indicated by serum progesterone in the luteal phase of the treatment cycle.

One cycle of treatment was administered. Treatment was not to exceed 14 days unless follicle size (≥ 14 mm) indicated imminent follicular maturation.

Patient Population

Eligible patients included premenopausal women with hypogonadotropic hypogonadism, aged 18 to 39 years, who desired pregnancy. Patients were required to have low serum values of FSH (< 5 IU/L), LH (< 1.2

IU/L), and estradiol ($E_2 < 60$ pg/mL), an endovaginal pelvic ultrasound scan showing (i) no clinically significant uterine abnormality, (ii) no ovarian tumor or cyst, and (iii) ≤ 13 follicles with mean diameter ≤ 10 mm in the largest section through each ovary, a Body Mass Index (BMI) between 18.4 and 31.4 kg/m² and a negative response to progesterone challenge test. Additionally, patients could not have systemic disease, or a previous history of severe ovarian hyperstimulation syndrome (OHSS).

Patient Disposition

A total of 39 patients were randomized and treated in this study. One patient terminated the study after four days of treatment due to an adverse event (rash). This non-serious event occurred in a patient receiving 75 IU of Luveris™.

Safety Results

A total of 44 events were recorded in 13 (33.3%) patients. The most frequently reported AEs (occurring in 2 or more patients overall) were abdominal pain, flatulence, nausea, headache, injection site reaction, and ovarian cyst.

All except one of the 44 adverse events were judged by the Investigator to be mild or moderate in severity. Only one event was judged to be severe; this event was ovarian hyperstimulation in one (8.3%) placebo patient. Although the event was considered to be severe, the Investigator did not feel that it qualified as serious. Twelve of the 17 events (70.6%) reported in the placebo group were thought to be possibly or probably related to study drug. Twelve of the 27 events (44.4%) in the 75 IU r-hLH group were thought to be possibly or probably related to study drug.

One patient who was randomized to and received placebo experienced one serious adverse event after the completion of treatment related to pregnancy, which resulted in two serious adverse events in the offspring. The patient was hospitalized and delivered twins prematurely via emergency C-section at twenty-four weeks gestation. The weights of the twins were 636 g (Infant A) and 534 g (Infant B). Subsequent to the delivery, one of the twins (Infant A) was diagnosed as septic with *E. coli*, and developed complications including intracerebral hemorrhage. The infant was removed from life support two days after the birth. An ultrasound performed on Infant B did not indicate any hemorrhaging.

A total of 27 patients received treatment with r-hLH. The median amount of r-hLH exposure was 900 IU and ranged from 300 to 1275 IU. The median duration of r-hLH treatment was 12 days with a range of 4 to 17 days.

Efficacy Results

The primary endpoint of the study was follicular development rate. The follicular development rate (66.7%) was statistically significantly higher ($p=0.023$) in the 75 IU r-hLH evaluable group when compared to the placebo evaluable group (20.0%). In the ITT population analysis, 65.4% patients in the r-hLH group achieved follicular development and 15.4% patients in the placebo group achieved this endpoint; this difference was statistically significant ($p=0.006$).

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

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

/s/

Ridgely C. Bennett
3/1/02 02:22:39 PM
MEDICAL OFFICER

Shelley Slaughter
3/1/02 02:28:51 PM
MEDICAL OFFICER
I concur. See also Acting Deputy Division Director Team
Leader Memo.