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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-322

Medical Review(s)

Luveris[®]
Team Leader Memorandum
Complete Response to Not-Approvable Action

NDA: 21-322

Drug: Luveris[®] (recombinant human Luteinizing Hormone [r-hLH])

Indication: **Original NDA:-**
Concomitant administration along with recombinant human follicle stimulating hormone (r-hFSH) for the induction of ovulation in infertile women with severe LH (< 1.2) U deficiency.

Revised Final:
Concomitant administration along with Gonaf[®] (follitropin alfa for injection) for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2). A definitive effect on pregnancy in this population has not been demonstrated. The safety and effectiveness of concomitant administration of Luveris[®] with any other preparation of recombinant human FSH or urinary human FSH is unknown.

Dosage/Form/Route: 75 IU sterile lyophilized powder to be reconstituted with 1 ml Sterile Water for Injection. A single 75 IU dose is administered via subcutaneous injection once daily until estradiol and ultrasound monitoring indicate that 7 hCG should be given to complete follicular development and effect ovulation. FSH should be administered concomitantly with Luveris[®]

Applicant: Serono Laboratories, Inc
Original Submission Date: May 01, 2001
N-000BZ Complete Response May 25, 2004
Primary Review Completed: September 28, 2004
Concurrence October 06, 2004
Date of Memorandum: October 06, 2004

Background and Regulatory History:

On March 01, 2002, the Agency sent to Serono a Not-Approvable decision for NDA 21-322 for Luveris[®] for the indication of induction of ovulation in hypogonadotropic hypogonadal infertile women with severe LH (< 1.2) U deficiency. The reader is referred to the primary Medical Officer and Team Leader reviews, dated March 01, 2002 for details on the clinical team's findings on efficacy and safety. A post-decision meeting was held with Serono on May 10, 2002.

At that meeting the Division proposed that the Sponsor conduct a new Phase 3 study that would address ovulation rates for subjects receiving the 75 IU dose and one or more lower doses. Instead the Sponsor proposed to submit the data from Study 21415, an extension study to Study 21008. The Division relayed to the Sponsor that post-hoc analyses on Study 21415 were insufficient to address the Division's concerns with efficacy and that Study 21415 was unacceptable as a "pivotal" study. The Division conveyed to the Sponsor that they had the options of either appealing the Division's decision to the Office of Drug Evaluation 3 or they could submit for review a protocol for a new study.

On January 09, 2003, a second post-decision discussion via teleconference was held with the Sponsor. The Division reiterated its position from the May 10, 2002 meeting that efficacy had not been established and the Sponsor could appeal the decision or conduct a new study. The Sponsor was also given the additional option of discussing their application at an upcoming meeting of the Advisory Committee for Reproductive Health. The Sponsor opted to have the application discussed before the Advisory Committee. Luveris® was discussed on September 30, 2003, the second day of a two-day meeting of the Reproductive Health Committee. After hearing presentations from experts in Reproductive Endocrinology on the subject of female hypogonadotropic hypogonadism as well as the presentations of the Division and the Sponsor on the efficacy data for Luveris®, the Committee was asked to discuss the application and vote on specific questions. The Committee voted 15 to 0 that the Sponsor's data did not demonstrate efficacy for Luveris® in ovulation induction when the primary endpoint was ovulation rate. The Committee voted 8 to 7 that the Sponsor's data demonstrated efficacy for Luveris® in ovulation induction when the primary endpoint was follicular development. Finally, the Committee voted 11 to 3 (one committee member had left the proceedings) that the Sponsor's data demonstrated efficacy for Luveris® for follicular development when the primary endpoint was follicular development.

Following the Advisory Committee Meeting, the Division committed to taking a closer look at Study 21415. The Sponsor formally submitted Study 21415 on April 28, 2003 as Amendment N-000 BZ. The clinical team's conclusion (See Medical Officer's review with Team Leader concurrence on September 09, 2003 and Medical Officer Team Leader review on April 22, 2004) was that data collected in Study 21415, a post-hoc, non-randomized, open-label study, did not provide sufficient additional evidence to support efficacy for Luveris® in ovulation induction and pregnancy.

A Type A meeting was held with Serono on January 09, 2004 to continue discussions on the September 30, 2003 Advisory Committee Meeting. At that meeting the DRUDP Division Director agreed to re-review the application, the regulatory history, scientific data, and the Advisory Committee transcript to make a reconsideration of the Division's prior decision of Not-Approvable.

On April 30, 2004, the Division Director, in consultation with the Deputy Office Director for Office of Drug Evaluation 3, concluded that Luveris® could be approved under provisions in the accelerated approval regulation, Subpart H (21CFR §314.510) that allow granting of marketing approval based on a surrogated endpoint or an effect on a clinical endpoint other than survival or irreversible morbidity. The Division Director further concluded that in this orphan population of women with severe LH deficiency ($LH \leq 1.2$), the surrogate endpoint of follicular development (as defined by the Sponsor) was reasonably likely to predict clinical benefit. In the regulatory letter of April 30, 2004, the Division Director stated that approval of NDA 21-322 under 21 CFR 314.510 would be subject to the requirement that the Sponsor conduct an adequate and well-controlled postmarketing study to verify and describe the clinical benefit of Luveris® with respect

to pregnancy and that FDA may withdraw marketing approval for Luveris® if a postmarketing study fails to verify clinical benefit or if the Sponsor fails to perform the required postmarketing study with due diligence. Finally, the April 30, 2004 letter listed the requirements for the Sponsor to pursue approval under Subpart H and provide a complete response to the Not-Approvable letter of March 01, 2002. These included:

1. The final study report for Study 21415
2. A protocol proposal for a Phase 4 postmarketing study to confirm clinical benefit in profoundly LH-deficient infertile women with hypogonadotropic hypogonadism. The proposed trial design should be a randomized, double-blind, placebo controlled trial with pregnancy as the primary endpoint. In this trial, a fixed dose of Luveris® is to be concomitantly administered with a titratable dose of r-hFSH. Prior to approval, agreement must be reached on the overall study design and analysis plan, as well as the proposed time for initiation of patient enrollment, and submission of the final study report.
3. Draft professional labeling
4. A safety update and summary of the worldwide safety experience with the drug.

A complete response from Serono was received on June 03, 2004.

Brief Summary of Efficacy Conclusions of the Medical Officer Team

Studies 21008, 6253, 6905, 7798 and 8297 were all reviewed under NDA 21-322 during the original review period. The reader is referred to the reviews of the Medical Officer dated March 01, 2002 and the Medical Officer Team Leader dated March 01, 2002 for a detailed discussion of the findings from these studies. The conclusion of the clinical team was that the data collected in the pivotal Phase 3 trial, Study 21008, and the four supportive Phase 2 trials, Studies 6253, 6905, 7798 and 8297 did not provide sufficient evidence to support the efficacy of the 75 IU/day dose of Luveris® for follicular development or ovulation induction in hypogonadotropic hypogonadal women with infertility.

Study 21415 was submitted as Amendment N-000-BS, dated April 28, 2003, and reviewed by medical officer (see review dated September 09, 2003) and Medical Officer Team Leader (see review dated April 22, 2004). The reader is referred to these reviews for details on the efficacy and safety findings. The clinical team concluded that the data collected in Study 21415 does not provide sufficient additional evidence to support efficacy for Luveris® in ovulation induction and pregnancy. The final study report for Study 21415 was included as part of Serono's complete response to the Not-approvable action for NDA 21-322. The Medical Officer's review dated, September 28, 2004 concludes that Study 21415 is inadequately designed and does not provide sufficient evidence of efficacy for Luveris®.

Conclusions and Recommendations

The data collected in Studies 6253, 6905, 7798, 8297, 21008 and 21415 do not provide sufficient evidence to support efficacy for Luveris® in ovulation induction and pregnancy. I concur with the clinical reviewer and I continue to recommend that this NDA not be approved. The Division Director has concluded that Luveris® could be approved under provisions in the accelerated approval regulation, Subpart H (21CFR §314.510) that allow granting of marketing approval based on a surrogate endpoint. He has concluded that the surrogate endpoint of Follicular Development is **reasonably likely** to predict clinical benefit for pregnancy in this orphan population of women with severe LH deficiency (LH<1.2).

Labeling

Draft labeling was submitted with the complete response. Given the above consideration by the Division Director and recognition that this drug product is most likely going to be approved, I offer the following labeling recommendations to help the practitioner and patient in the use of this product:

Clinical Studies subsection

1. All reference to study 21415 should be removed from the label. This study was not of the design and quality usually relied on to provide labeling information. As such the presentation of efficacy information from this study is misleading to both patient and practitioner.
2. Tables 3 and 5 should be labeled as "Study 6253 (Population: Intent to Treat)" and "Study 21008 (Population: Intent to Treat)", respectively. These tables should only present the respective ovulation rates for this study and should include the statistical significance of these values. I feel very strongly that the practitioner and patient should be aware that even though the label suggest that Luveris® was statistically superior to placebo for follicular development (this was not shown in the FDA analysis) this did not translate into the product being statistically significantly superior to placebo for ovulation. Table 3 should not present any information on pre-ovulatory estradiol rates or endometrial thickness as these do not help guide the practitioner or patient on use of this product. The measure of endometrial thickness was controlled by center and is an experimental endpoint.
3. Table 4 "Study 21008 Follicular Development Rate (Population: Intent to Treat)" should be modified to help the patient and practitioner better understand its significance. As the Sponsor now has it displayed it is not intuitive as to how the results, particularly when expressed as percentages, were obtained. My recommendation for improvement of this table is as follows:

Table 4. Study 21008 Follicular Development Rate (Population: Intent to Treat)

Follicular Development Rate	Placebo & Gonol-f® (n=13) n (%)	75 IU Luveris® & Gonol-f® (n=26) n (%)
Cycle Cancellation Due to Risk of OHSS^(a) considered as Success		
Successful Follicular Development	2 (15%)	17 (65%)
Failed Follicular Development	11 (85%)	09 (35%)
p-value vs. placebo ^(b)		0.006
Cycle Cancellation Due to Risk of OHSS^(a) considered as Failure		
Successful Follicular Development	1 (8%)	11 (42%)
Failed Follicular Development	12 (92%)	15 (58%)
p-value vs. placebo ^(b)		0.034

(a) Cycles were cancelled due to the risk of OHSS when the E2 level exceeded 1,100 pg/mL and/or ≥ 3 follicles were ≥ 15 mm in diameter

(b) Fisher's Exact Test

Adverse Reactions subsection

4. Table 7 the adverse events table reporting all such events in $\geq 2\%$ patients during use of Luveris® in all cycles for all hypogonadotropic hypogonadal patients should include data from studies 6905, 6253, 7798, 8297, 21008 and 21415.
5. There should be a patient package insert in plain language to guide patient use.

Proposed Phase 4 Study

As part of the complete response to the March 01, 2002 Not-Approvable Action and to be considered under Subpart H, the Sponsor has submitted a protocol, titled "A phase IV clinical trial to confirm the efficacy of the 75 IU dose of Luveris® vs. Placebo when co-administered with follitropin alfa for induction of follicular development and pregnancy in hypogonadotropic hypogonadal women with profound LH deficiency, as defined by a baseline LH level <1.2 ". This Phase 4 study will address the efficacy of Luveris® in helping women with hypogonadotropic hypogonadism achieve pregnancy. The clinical team has recommended a number of modifications to the original protocol as submitted in the complete response. These have been communicated to the Sponsor. The recommendations determined to be most vital to the success of this Phase 4 study are as follows:

1. The study should be designed to look for the lowest effective dose and, therefore, a dose of Luveris® lower than 75 IU (we would suggest the Sponsor consider 37.5 IU) should be evaluated in addition to the 75 IU dose.
2. The primary efficacy analysis should be an intent-to-treat analysis of the time from randomization to the occurrence of a clinical pregnancy (a gestational sac with fetal heart motion on vaginal ultrasound at 6 weeks post-embryo transfer). To demonstrate efficacy, the lower bound of the two-sided 95% or one-sided 97.5 % confidence interval should exclude a difference greater than one month.
3. The per cycle clinical pregnancy rate analyses and cumulative cycle analyses should be considered secondary analyses.
4. The secondary endpoint of Follicular Development should be defined by a serum estradiol ≥ 200 pg/ml and a mid-luteal progesterone ≥ 10 ng/ml values which more closely reflect normal development of follicles destined to ovulate.
5. Patients who have had their Luveris® dose titrated should be excluded from this analysis.
6. Patients who have had their cycles cancelled for the risk of ovarian hyperstimulation syndrome and who do not demonstrate a clinical or ongoing pregnancy should be considered as treatment failures. Follicular development and ovulation should not be assumed to have occurred when a positive pregnancy test (serum beta-hCG greater than 10 MIU/ml) is obtained.
7. The specific infertility diagnosis should be recorded in detail for each patient entering the trial.
8. Patients who receive in vitro fertilization, intracytoplasmic injection or any other Assisted Reproductive Technology other than IVF should be excluded from the study.

Serono has agreed to incorporate the above recommendations for the Phase 4 Study.

Shelley R. Slaughter, M.D., Ph.D.
Reproductive Medical Officer Team Leader

cc: Division File NDA 21-322
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/s/

Shelley Slaughter
10/7/04 11:54:25 AM
MEDICAL OFFICER

CLINICAL REVIEW

Luveris®

NDA 21-322

CLINICAL REVIEW

Medical Officer's Review
NDA 21-322/SN-000-BZ

Date Response Submitted: May 25, 2004
Date NDA Received: June 3, 2004
Review Finalized: September 28, 2004

Medical Officer's Review (Original Review)

Sponsor: Serono, Inc.
One Technology Place
Rockland, MA 02370

Drug Name:
Generic: lutropin alfa for injection
Trade: Luveris®
Chemical: recombinant human luteinizing hormone (r-hLH)

Pharmacologic category: Infertility
Dosage Form: 75 IU of sterile lyophilized powder with 1 vial of sterile water
Strength: A single 75 IU dose of Luveris® would be administered via subcutaneous injection once daily until estradiol and ultrasound monitoring indicate [] human chorionic gonadotropin (hCG) should be given to complete follicular development and effect ovulation. FSH at 75 to 150 IU per day should be administered concomitantly with Luveris®. Treatment duration should not normally exceed 14 days unless signs of imminent follicular development are present.

Proposed Indication: Concomitant administration along with recombinant human follicle stimulating hormone (r-hFSH) for the induction of ovulation in hypogonadotropic hypogonadal infertile women with severe LH (< 1.2 IU/L) [] deficiency.

Related Submission: IND 44,108

Related Documents For the Original NDA Application:
The initial NDA submission for Luveris® (lutropin alfa) was received May 1, 2001.
The original Medical Officer's Review of NDA 21-322 was finalized February 25, 2002.
The original Clinical Pharmacology and Biopharmaceutical Review finalized on April 30, 2001.
OPDRA Review of tradename Luveris® dated December 17, 2001.

CLINICAL REVIEW

Related Documents

(continued):

The Acting Division Director Team Leader's Memo was finalized March 1, 2002.

The original Agency letter containing the Non-Approval Action was dated March 1, 2002.

Minutes from a Type A Meeting held May 10, 2002.

Minutes from a second Type A Meeting held January 9, 2003.

An Amendment containing Study 21415 was originally submitted April 28, 2003 as N-000-BZ to NDA 21-322.

A medical officer's review of the Amendment N-000-BZ for study 21415 was finalized September 9, 2003.

A Reproductive Advisory Committee meeting held to discuss the Non-Approvable Action on September 30, 2003.

Minutes from a third type A meeting was January 9, 2004.

Division's Advice Letter requesting a phase 4 protocol commitment dated April 30, 2004.

Sponsor's correspondence with proposal for a phase 4 study dated April 30, 2004.

Division's General Correspondence Letter commenting on a proposed phase 4 protocol dated May 24, 2004.

Sponsor's draft of proposed Luveris® labeling submitted May 25, 2004. (NDA 21-322/N-000-DZ).

Division's Advice Letters on the proposed phase 4 protocol and label both dated July 8, 2004.

Sponsor's revised label and protocol in response to the Division's Advice Letters dated July 23, 2004. (NDA 21-322/N-000-BM).

Division's additional comments on label dated August 26, 2004.

Sponsor's revised label submitted September 7, 2004. (NDA 21-322/N-000-BL)

An Annual Report (Serial No. 165-YY) submitted to the IND (#44,108) on March 5, 2003.

A Safety Update submitted to NDA 21-322 (Serial No. N-000-SU) on July 19, 2004.

CLINICAL REVIEW

Table of Contents

Table of Contents	4
Executive Summary	7
I. Recommendations	7
A. Recommendation on Approvability	7
B. Recommendation on Phase 4 Studies and/or Risk Management Steps	7
II. Summary of Clinical Findings	7
A. Brief Overview of Clinical Program	7
B. Efficacy	15
C. Safety	16
D. Dosing	16
E. Special Populations	16
Clinical Review	17
I. Introduction and Background	17
A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups	17
B. State of Armamentarium for Indication(s)	17
C. Important Milestones in Product Development	17
D. Other Relevant Information	18
E. Important Issues with Pharmacologically Related Agents	20

CLINICAL REVIEW

II.	Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews.....	21
III.	Human Pharmacokinetics and Pharmacodynamics.....	21
	A. Pharmacokinetics	21
	B. Pharmacodynamics	21
IV.	Description of Clinical Data and Sources	22
	A. Overall Data	22
	B. Tables Listing the Clinical Trials.....	22
	C. Postmarketing Experience	22
	D. Literature Review.....	23
V.	Clinical Review Methods.....	23
	A. How the Review was Conducted	23
	B. Overview of Materials Consulted in Review.....	23
	C. Overview of Methods Used to Evaluate Data Quality and Integrity	24
	D. Were Trials Conducted in Accordance with Accepted Ethical Standards.....	24
	E. Evaluation of Financial Disclosure	24
VI.	Integrated Review of Efficacy.....	24
	A. Brief Statement of Conclusions	24
	B. General Approach to Review of the Efficacy of the Drug.....	25
	C. Detailed Review of Trials by Indication	25
	D. Efficacy Conclusions	34

CLINICAL REVIEW

VII. Integrated Review of Safety	35
A. Brief Statement of Conclusions	35
B. Description of Patient Exposure	35
C. Methods and Specific Findings of Safety Review	35
D. Adequacy of Safety Testing.....	41
E. Summary of Critical Safety Findings and Limitations of Data	41
VIII. Dosing, Regimen, and Administration Issues	42
IX. Use in Special Populations	43
A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation.....	43
B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy	43
C. Evaluation of Pediatric Program.....	43
X. Conclusions and Recommendations	43
A. Conclusions.....	43
B. Recommendations.....	44
XI. Appendix	45
A. Efficacy Tables from Study 21415	45
B. Safety Tables from Study 21415 and the Safety Update	51
C. Overview of Completed Clinical Trials for NDA 21-322	53
D. References.....	56
E. Review of New Phase 4 Protocol.....	58
F. Study Design of Phase 4 Protocol (Figure 1).....	66

CLINICAL REVIEW

Clinical Review Section

Clinical Review for NDA 21-322

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The original phase 2 and 3 studies were submitted as proof of efficacy during the first review cycle. In this reviewer's opinion, the efficacy of Luveris® (in terms of ovulation and clinical pregnancy) has not been adequately demonstrated to date by the Sponsor. The Division Director has concluded that a submission meeting the recommendations as outlined in the April 30, 2004 letter is Approvable based on Subpart H. The Sponsor has satisfactorily met the conditions with the submission of the final study report for Study 21415, a safety update, and a commitment for a phase IV study for Luveris® as well as the data from the original Phase 2 and 3 studies. The proposed Phase 4 study to satisfy the requirement under §314.510 that Luveris® be studied further to verify and describe the clinical benefit, when completed, should adequately address in this orphan population of women with severe hypogonadotropic hypogonadism whether or not Luveris® demonstrates efficacy for pregnancy.

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

In this reviewer's opinion, the protocol for the phase 4 (post-approval) study, after several revisions, is now adequate. (See reviewer's initial comments on the outline of the proposed phase 4 protocol sent in a General Correspondence letter dated April 30, 2004.) The Sponsor has also now agreed to evaluate a lower dose (less than 75 IU) of Luveris® in the phase 4 study.

II. Summary of Clinical Findings

A. Overview of Clinical Program

A pre-IND meeting May 21, 1992 was held with the Division to discuss the designation of recombinant human luteinizing hormone (r-hLH) as an orphan drug product for the treatment of women with WHO group I anovulation (idiopathic hypogonadotropic hypogonadism). Hypogonadotropic hypogonadism is a rare condition estimated by the Sponsor to be 14,740 cases per year in women in the United States. Luveris® is lyophilized powder that contains a heterodimeric glycoprotein whose alpha and beta subunits are very similar to pituitary-derived luteinizing hormone (LH).

CLINICAL REVIEW

Clinical Review Section

Overview of the Clinical Program (continued):

At the pre-IND meeting, it was agreed that two identical clinical studies of equal size (32 patients in each study) using the same protocol [one in the United States (Study 6905) and one in Europe (Study 6253)] would be performed in women with WHO group I anovulation.

Women with WHO group I anovulation are amenorrheic, with little or no endogenous estrogen activity who do not respond to withdrawal bleeding when suitable progesterone is administered. Studies 6905 and 6253 were to serve as the basis to support an application for ovulation induction in these hypogonadotropic women. The Sponsor submitted only one protocol for a clinical trial to IND 44,108 on December 8, 1993 to be conducted in the United States (Study 6905). Study 6905 was entitled "An open, randomized, dose-finding multi-center study to determine the minimal effective dose and to assess the safety of r-hLH to support r-FSH – induced follicular development in anovulatory women with hypogonadotropic hypogonadism". No mention of the European study protocol was made in the IND, and this protocol was not submitted to the Agency prior to the completion of the European study. Per the Sponsor, two significant revisions were made in the "Inclusion Criteria" of Study 6905 to make the study population more closely match the endocrine profile of the hypogonadotropic patients treated in clinical practice in the U.S. Study 6905 was revised and submitted in an amendment on July 20, 1994 before the start of the study:

1. The need to have a negative progesterone challenge test was replaced by the requirement for a serum estradiol concentration of less than 60 pg/mL.
2. The requirement for serum FSH and LH levels below 5 IU/L was replaced by the requirement to be at or below the 50th percentile of normal range for the follicular phase established. (The central laboratory for hormonal parameters for Study 21415 was reported as \bar{C} \bar{J})

In contrast to these inclusion criteria, Study 6253 (the European study) used a requirement of a serum LH less than 1.2 IU/L. Therefore, the sub-populations of women with hypogonadotropic hypogonadism based on endogenous levels were **different** for the two studies even though the pre-IND agreement was that the clinical trials would be identical. The primary endpoint for both studies was follicular development as defined by three parameters (appropriate estradiol levels, ultrasound follicular measurement, and mid-luteal progesterone levels) all of which had to be satisfied. A request for orphan status, subsequently approved, was submitted January 14, 1994.

CLINICAL REVIEW

Clinical Review Section

In the pre-NDA briefing document submitted on June 12, 1998, the proposed indication was stated as "treatment of women with chronic anovulation due to hypogonadotropic hypogonadism (H.H.)." Only the two clinical studies (Study 6905 and Study 6253) were submitted as part of the briefing document. The Sponsor requested that the Agency confirm that the data from U.S. Study (6905) and European Study (6253) were adequate for filing and approval of an NDA. The primary efficacy endpoints for both studies 6905 and 6253 was "follicular development" as defined by three parameters, (follicle size as measured on ultrasound, pre-ovulatory serum estradiol levels, and mid-luteal serum progesterone levels), all of which had to occur.

- The Sponsor's analysis showed that in Study 6253, the 75 IU of Luveris® was numerically better than 25 IU of Luveris® and placebo for follicular development in women with LH <1.2 IU/L. In Study 6905, the Sponsor's analysis showed that both 25 IU of Luveris® and 75 IU of Luveris® were effective for follicular development of women with hypogonadism whose LH levels were less than 13.3 IU/L.
- The Division's analysis of Study 6905 revealed that 25 IU of Luveris® was numerically better than 75 IU of Luveris®, and placebo was as efficient as 75 IU of Luveris®. Clearly in the patient population studied, Luveris® was not shown to be effective in treating hypogonadotropic hypogonadism as "usually diagnosed in the United States" (per the Sponsor). Furthermore, Study 6253 (the European study) revealed that (in contrast to the United States study) that 75 IU of Luveris® was numerically better than either 25 IU of Luveris® or placebo. An additional subset analysis of patients in Study 6905 with an LH of less than 1.2 IU/L failed to confirm the findings of Study 6253.

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

- Study 6253 (European) and Study 6905 (United States) were originally designed as dose finding studies with identical protocols and numbers of subjects
- Both studies were considered equally informative by the Division because results were quite different in the two studies. An additional study would be needed to demonstrate efficacy of the selected minimal dose.
- Neither study showed a significant difference in efficacy at the projected endpoints; the most positive item finding was the dose-related trend in the ITT analysis of Study 6253.
- Although both Study 6905 and Study 6253 were designed as dose-finding studies, the studies reached different dosing conclusions when low LH patients were separated out.
- The effect of Luveris® in Study 6905 may have been masked by the broader inclusion criteria.
- More data would be needed before the NDA was fileable.

CLINICAL REVIEW

Clinical Review Section

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 then provided a supplemental pre-NDA meeting package on November 18, 1998 containing new data from two additional clinical trials carried out in Europe. Study 7798 was conducted in Germany on a profoundly LH deficient population (LH less than 1.2 IU/L) while Study 8297 was conducted in Spain in a moderately LH deficient population (LH below or within the normal range). These two new clinical trials, Studies 7798 and 8297, were not designed to determine the minimal effective dose, had different patient populations, and did not use doses less than 75 IU.

The Deputy Director of ODE II and the Division met again with the Sponsor on November 30, 1998. The Division included in the discussion the following points:

- Two dose finding studies using the same protocol were originally proposed at the pre-NDA meeting; neither submitted Studies 6905 or 6253 were initially designed as pivotal trials, but dose finding studies.
- Studies 6905 and 6253 were not powered on any criteria other than the limited size of the patient population.
- A trend test was proposed as the 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. The FDA considered these trend tests to be exploratory tests and not significant for a pivotal trial.
- The European Study 6253 was significantly different from the U.S. Study 6905, with Study 6905 having broader inclusion criteria for patients to be enrolled.

The Sponsor reiterated their position that the 75 IU dose was chosen because it was optimal. The Sponsor was told that if the application was filed, it could be taken to an advisory committee meeting. Further communications from the Sponsor on December 16, 1998 stated that Studies 6253 and 7798 would form the basis of their proposed NDA.

On February 23, 1999, a teleconference with the Sponsor was held to discuss the fileability of their proposed NDA. The following points were discussed:

- The current database includes efficacy data from a placebo-controlled trial involving 11 patients who received 75 IU of Luveris® compared to 9 who received the placebo – this is insufficient for filing an NDA.
- The **clinical primary endpoint should be the ovulation rate** in a one-month treatment cycle.

CLINICAL REVIEW

Clinical Review Section

The Sponsor was informed at the February 1999 teleconference that:

- The product labeling would include information that the product is not effective in patients with LH levels greater than 1.2 IU/L if the data from these patients does not show efficacy.
- If a study comparing the 75 IU dose of LH with historical control data is planned, the protocol should be submitted for comment.
- The Sponsor could propose a new phase 3 clinical trial with wider inclusion criteria (for patient populations typically considered for Luveris® treatment) 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 less than 1.2 IU/L all of whom desired pregnancy.

The Sponsor then proposed a new protocol (21008) for a Phase III clinical trial and this proposal was submitted to the IND (44,108) on March 22, 1999. A teleconference with the Sponsor was held on May 3, 1999. Decisions reached included:

- The estradiol and progesterone levels proposed as cut-offs for follicular development would be re-evaluated and a valid argument for the proposed levels would be subject to review.
- The estimated success rate would be recalculated for each treatment group using the new criteria since the progesterone (and possibly) estradiol group used to determine treatment success may be changed.
- The sample size for the new pivotal study (21008) would reflect the revised estimates of the anticipated success rate and a placebo arm would be added.

A pre-NDA meeting was held with the Sponsor on December 12, 2000 to discuss the completion of an additional Phase III study that the Division had requested (Study 21008). At that meeting the Division acknowledged that Study 21008 would be an acceptable double-blind, placebo-controlled, randomized trial. The Division did discuss with the Sponsor that serum LH levels would be used to stratify analyses of the data. NDA 21-322 was received on May 1, 2001 and filed on June 30, 2001.

Study 21008 was a randomized, double-blind, placebo-controlled multi-center study conducted in 25 multinational centers. The Division had made a **strong recommendation** to the Sponsor that **only ovulation rate** (as determined by the percentage of subjects achieving a mid-luteal progesterone level of greater than 10 ng/mL) **should be used as the primary endpoint**. The Sponsor chose not to follow the Division's recommendation in the designation of the primary endpoint evaluated. Of note, the clinical review also found that women who had their cycle cancelled for the risk of ovarian hyperstimulation syndrome were being counted as a success.

CLINICAL REVIEW

Clinical Review Section

The acceptance of an adverse event resulting in cycle cancellation being counted as a success was not acceptable to the Division. As a result of the difference in determining the criteria for success for the primary endpoint, the results of the Sponsor's analysis and the Division's analysis differ significantly.

- The Sponsor's evaluable patient analysis of Study 21008 showed that 67% of patients receiving 75 IU of Luveris® achieved follicular development compared to 20% of patients receiving placebo. This analysis counted as successes treatment cycles cancelled for the risk of development of ovarian hyperstimulation syndrome (OHSS).
- The Division's intent-to-treat (ITT) analysis of Study 21008, (which counted cycle cancellations as failures), showed that only 38% of patients receiving 75 IU of Luveris® achieved follicular development compared to 8% of patients receiving placebo. Of note, the Sponsor had expected that an effective dose of Luveris® would result in a 90% follicular development rate in Luveris® treated patients, and both analysis of the primary endpoint in Study 21008 fell short of this expectation.

The initial Medical Officer Review was completed on February 25, 2002 using the five submitted clinical trials (Studies 6905, 6253, 21008, 7798, and 8297) in which a total of 173 subjects participated. The Medical Officer concluded that the application for Luveris® should not be approved, as the clinical data did not demonstrate efficacy of Luveris®. Furthermore, the Medical Officer judged that none of the five clinical trials demonstrated that the treatment effect of Luveris® was clinically or statistically substantial.

The Division's objections to Approval of this NDA were:

- The Sponsor continued to discuss "follicular development" as the primary efficacy endpoint in Studies 21008 and 6253 despite the fact that they were informed February 23, 1999 (one year before Study 21008 began) that the **primary efficacy endpoint should be ovulation.**
- In Study 21008, the Sponsor included a patient who was cancelled due to a risk of ovarian hyperstimulation syndrome. In the Division's re-analysis of the data, (using the Sponsor's criteria for follicular development), counting patients that had ovarian hyperstimulation syndrome as a failure and not a success, the p-value for the trial is **0.063 was not significant.**

Thus, even with the use of "follicular development" as a surrogate endpoint there was insufficient evidence to conclude that the Luveris® 75 IU treatment arm was significantly different from placebo.

The Acting Deputy Division Director concurred with the Not Approvable decision on February 28, 2002 and a Not Approvable action letter was sent on March 1, 2002.

CLINICAL REVIEW

Clinical Review Section

A meeting to discuss the Not Approvable action letter was held with the Sponsor on May 10, 2002. At this meeting, the Division recommended that the Sponsor propose a new phase III trial. The trial would include one or two doses lower than the proposed 75 IU dose. The Sponsor proposed instead to submit an open-label, non-randomized, extension study (21415) that used patients recruited in study 21008. The data from study 21415 included additional ovulation and pregnancy data. The following comments were relayed to the Sponsor at the May 2002 meeting:

- The Division stated analysis of Study 21415 was insufficient to address efficacy concerns. The Division stated that the extension Study 21415 was unacceptable as a "pivotal study"
- The Division requested that the Sponsor provide full study report for the 75 IU group (Study 21415).
- The Division pointed out that the Sponsor had agreed previously with the Division that the requirement for proven efficacy of Luveris® would be that Luveris® is more effective than placebo

The Division conveyed the following two options to the Sponsor at the end of the May 2002 meeting:

- The Sponsor could appeal the Not Approvable action to the ODE III immediate office if they choose.
- The Sponsor could submit a protocol a new trial looking at ovulation rates to support efficacy for DRUDP to review.
- In addition, the Division recommended that the Sponsor should propose the dose or doses to be evaluated. The Division recommended that the Sponsor include one or two doses lower than the 75 IU as well as the 75 IU dose.

A second teleconference was held with the Sponsor on January 9, 2003 to continue the discussion on the Not Approvable action letter on March 1, 2002. At the January 2003 meeting, the Division reiterated the comments from the May 2002 meeting and relayed the following additional options to the Sponsor:

- An advisory committee meeting will be held over a two-day period in approximately six months to discuss assisted reproductive technology products in general and the not approvable action for Luveris®.
- The Sponsor can conduct another phase III study as previously discussed.
- The Sponsor was asked to formally submit Study 21415 to the NDA for review by the Division.

The Sponsor formally submitted Study 21415 on April 28, 2003 as Amendment N-000-BZ for review by the Division.

CLINICAL REVIEW

Clinical Review Section

The medical reviewer concluded that study 21415 was a post-hoc, non-randomized, open-label study that was inadequate to make any efficacy conclusions concerning Luveris® (See Medical Officer's review of N-000-BZ finalized September 9, 2003).

The Sponsor opted to have the application discussed before the Advisory Committee. Luveris® was discussed on September 30, 2003, the second day of a two-day meeting of the Reproductive Health Committee. After hearing presentations from experts in Reproductive Endocrinology on the subject of female hypogonadotropic hypogonadism as well as the presentations from the Division and the Sponsor on the efficacy data for Luveris®, the Committee was asked to discuss the application and vote.

The Committee voted 15 to 0 that the Sponsor's data did not demonstrate efficacy for Luveris® in ovulation induction when the primary endpoint was ovulation rate. The Committee voted 8 to 7 that the Sponsor's data demonstrated efficacy for Luveris® in ovulation induction when the primary endpoint was follicular development.

Finally, the Committee voted 11 to 3 (one committee member had left the proceedings) that the Sponsor's data demonstrated efficacy for Luveris® for follicular development when the primary endpoint was follicular development. Following the Advisory Committee Meeting, the Division committed to reassessing Study 21415 in its process of addressing Sponsor's request for reconsideration of the Division's Not Approvable decision for NDA 21-322.

A Type A meeting was held with the Sponsor on January 9, 2004 to discuss the advice from the Advisory Committee held in September 2003. The Division Director agreed to review the application, the regulatory history, scientific data, and the Advisory Committee transcripts and make a decision regarding approvability.

On April 30, 2004, after a review of the NDA and the Advisory Committee transcripts, the Division Director concluded that Luveris® could be approved under Subpart H (CFR 314.510) as severe LH deficiency (serum LH < 1.2 IU/L) occurring in hypogonadal women could be defined as a serious condition in an orphan population. In addition, the Division Director concluded that follicular development (as defined by the Sponsor in the three previously submitted clinical studies: 6253, 6905 and 21008 and the initial study report for 21415) was an acceptable surrogate endpoint that could reliably predict the clinical benefit of pregnancy in this infertile hypogonadal population.

CLINICAL REVIEW

Clinical Review Section

The following four components for a complete response to the Non-Approvable Action were outlined for the Sponsor for approval under Subpart H:

1. The final study report for Study 21415 (A non-randomized supportive clinical study that examined ovulation and pregnancy rates in the hypogonadal population).
2. A proposed phase 4 protocol to address the Division's concerns about the efficacy of Luveris®.
3. A safety update with a summary of worldwide experience.
4. Draft professional labeling

B. Efficacy

Study 21415 was submitted to provide supportive evidence of efficacy in female hypogonadal patients with profound LH deficiency (serum LH < 1.2 IU/L). Study 21415 was an open-label, non-randomized, single arm extension study that recruited patients from a previous double-blind, randomized study (21008), but had not achieved a clinical pregnancy. The primary efficacy endpoint was achievement of adequate follicular development (a surrogate endpoint for clinical pregnancy) as defined by three conditions:

- i) at least one follicle with a mean diameter of \geq than 17 mm
- ii) pre-ovulatory serum estradiol levels of greater than 109 pg/mL
- iii) mid-luteal phase progesterone levels of \geq 7.9 ng/mL.

Study 21415 had a 35% clinical pregnancy rate in the first cycle (Luveris® treated subjects) and 29.6% per cycle clinical pregnancy rate. However, lack of a control arm and randomization in study 21415 makes the interpretation of this pregnancy rate difficult. In this reviewer's opinion, the flaws in Study 21415, (non-randomization, lack of a control arm and the open-label design) are significant. These trial design problems prevent Study 21415 from being an acceptable "pivotal study" that definitively demonstrated efficacy of Luveris® in association with recombinant human follicle stimulating hormone (r-hFSH) for the induction of ovulation in infertile patients with profound LH and FSH deficiency.

However, this reviewer notes that the Sponsor has provided data on pregnancy occurring in subjects treated with Luveris®, but one should use caution in the interpretation of that data given the significant flaws in this study. Therefore, a confirmatory phase 4 study is still required to conclude that the addition of r-hLH to r-hFSH improves clinical pregnancy rates in this female hypogonadal population with severe LH deficiency (Serum LH < 1.2 IU/L). The design of the proposed phase 4 study will not identify the lowest effective dose of Luveris®.

CLINICAL REVIEW

Clinical Review Section

C. Safety

The supportive clinical trial (Study 21415) and submitted safety update (dated 19-Jul-04) provide additional safety data that shows no unexpected adverse events or trends. This safety data from Study 21415 and the update is similar to the clinical safety database information from the five previous clinical trials submitted to NDA 21-322. The safety database information for Luveris® is acceptable, although the patient numbers are very small. The additional clinical safety information on Luveris® provided in the Study 21415 appears to support an acceptable safety profile in the limited patient population of hypogonadal infertile women. This reviewer recommends that the Sponsor also submit the results of the Phase IV study when completed to further evaluate the effects of Luveris® on the rate of ovarian hyperstimulation syndrome.

D. Dosing

The Sponsor's proposed dose of 75 IU/day has not been established as the minimum effective dose. A dose of 25 IU may be sufficient as demonstrated in Study 6905. There is no evidence that a dose higher than 75 IU/day is more effective than 75 IU/day. Theoretically, studied doses of up to 225 IU/day have the potential for increasing the risk of adverse events, although the database with these doses is extremely sparse. In addition, there may be as yet undocumented efficacy or safety issues when Luveris® is mixed with other gonadotropin products.

E. Special Populations

This drug is seeking approval for conditions that occur only in women. The indication of ovulation induction does not apply to pediatric or geriatric populations. This drug is contraindicated in pregnancy.

CLINICAL REVIEW

Clinical Review Section

Clinical Review

I. Introduction and Background

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

Established Name: lutropin alfa for injection
Proposed Trade Name: Luveris®
Drug Class: Infertility
Sponsor's Proposed Indication: Concomitant administration along with recombinant human follicle stimulating hormone (r-hFSH) for the induction of ovulation in hypogonadotropic hypogonadal infertile women with severe LH (< 1.2 IU/L) \pm γ deficiency.
Dosage/Form/Strength: 75 IU sterile lyophilized powder to be reconstituted with 1 ml sterile water for injection. A single 75 IU dose of Luveris® would be administered via subcutaneous injection in the abdomen once daily until estradiol and ultrasound monitoring indicate that human chorionic gonadotropin (hCG) should be given to complete follicular development and effect ovulation. FSH at 75 to 150 IU per day should be administered concomitantly with Luveris®. Treatment duration should not normally exceed 14 days unless signs of imminent follicular development are present.

B. State of Armamentarium for Indication(s)

Other urinary and recombinant products for follicular development and ovulation induction are available on the United States market. Luveris® would be the only LH-alone product (recombinant or urinary-derived) on the U.S. market. There are no approved drug products that have the indication of treatment of infertility in women with hypogonadotropic hypogonadism, although menotropins have historically been used "off label" for this indication.

C. Important Milestones in Product Development

Recognition of the therapeutic potential of gonadotropins began in the 1950's with the extraction and purification of human menopausal gonadotropins (both follicle stimulating hormone and luteinizing hormone) from both human pituitaries and urine sources. Successful clinical pregnancies resulting from the use of these human-derived gonadotropins were first reported in the 1960's. In the 1990's cells that are capable of producing biologically active LH in culture produced luteinizing hormone (LH). This recombinant derived LH is from *in vitro* cultured cells.

CLINICAL REVIEW

Clinical Review Section

D. Other Relevant Information

Hypogonadotropic hypogonadal women with abnormal gonadotropin secretion and amenorrhea may represent a spectrum of clinical disorders. The various types of clinical pathologies that cause hypogonadism result in different patterns of gonadotropin secretion (of luteinizing hormone and follicle-stimulating hormone) and even different modes of inheritance. The biochemical evaluation of patients with hypogonadotropic hypogonadism may be marked by gonadotropin levels that are undetectable, low, or apparently normal.¹ These differences in gonadotropin levels occur in hypogonadal patients, despite identical clinical presentation of amenorrhea and hypoestrogenism, and result in different responses to treatment regimes. The susceptibility of these hypogonadal patients to various treatment regimens may change between treatment cycles and over time.¹ The dynamic fluctuations in gonadotropin pulsation and varying response to treatment regimens further complicates outcome measurements in hypogonadal patients.¹

Previous small clinical infertility trials included patients with primary and secondary hypogonadotropic hypogonadism. The majority of these clinical trials were non-randomized, open-label, treatment cycle results from single clinical centers. One unique treatment, Lutrepulse® (IND 22,278 and NDA 19-687), was approved for use in women with a more broadly defined diagnosis of hypothalamic amenorrhea. Lutrepulse® used a pump to deliver pulsed intravenous Gonadotropin-Releasing Hormone (GnRH). In the literature, a comprehensive review stated that a total of over 500 cycles of GnRH therapy were published with an overall ovulation rate of approximately 90% and an overall conception rate of 27% per cycle.²

In the original NDA (19-687), the primary criterion of efficacy for Lutrepulse® in this “hypogonadotropic hypogonadal” population was **ovulation**. In two of the larger clinical trials, 22 of 26 (85%) and 10 of 11 (91%) of primary hypothalamic patients (defined as never having experienced a menstrual cycle along with deficient FSH and LH production) ovulated in the first treatment cycle. (NDA 19-678) These clinical trials from the 1980’s used historical controls, and did **not** define the specific levels of FSH and LH that were used to classify patients as “hypogonadotropic hypogonadism”. The cost of the pump and the limited number of patients who would require therapy restricted the overall therapeutic potential of Lutrepulse®. The need for constant intravenous access made this a less than desirable therapy for patients. In addition, technical problems with the pump resulted in Lutrepulse® being discontinued for commercial reasons.

Evidence for success for infertile hypogonadotropic women with human menopausal gonadotropin (hMG) and follicle stimulating hormone (FSH) products has been limited to non-randomized, open-label clinical trials using small groups of subjects.

CLINICAL REVIEW

Clinical Review Section

Other Relevant Information (continued):

These clinical trials of hypogonadotropic hypogonadal women had various protocol designs that assessed the outcomes of ovulation and pregnancy rates.

One **uncontrolled** study with 31 patients used a "flare protocol" (a combination of human menopausal gonadotropin and gonadotropin releasing hormone analogue) to treat hypogonadal infertility patients in 1990.³ The limited results of this **uncontrolled** study showed a biochemical pregnancy rate of 28% in 26 cycles.³ Another smaller **uncontrolled** clinical trial, published in 1989, used a group of hypogonadal and hypo-estrogenic female subjects.⁴ The treatment was pulsatile human menopausal gonadotropin administration via the subcutaneous route. A total of 8 patients with low endogenous estrogen were treated for 40 cycles. Ovulation occurred in 87.5% (35 of 40) of the total treatment cycles.⁴ Mild ovarian hyperstimulation was seen in 12.5% of cycles, and no severe ovarian hyperstimulation cases was noted in this hypo-estrogenic group.⁴

When purified follicle stimulating hormone became available in the 1990's, one study looked at hypogonadal subjects and compared the use of purified FSH and FSH/LH combinations to see if there was an improvement in ovulation and pregnancy rates with addition of the LH moiety. In a cross-over clinical study by Shoham in 1991, purified FSH yielded a lower ovulatory rate (33%) as compared to the FSH/LH combination therapy (89%).⁵ However, information from this trial was limited because it was open label, performed in only nine patients, and has not been repeated to date.

Reviewer's comments:

1. **Overall, the published clinical data using human menopausal gonadotropins to treat hypogonadal infertility patients is mainly from limited "clinical experience trials" rather than appropriately powered randomized, double-blind trials. Despite the lack of appropriately powered clinical trials, the use of human menopausal gonadotropins in hypogonadal infertility patients has become an accepted "off label" use in clinical practice.**
2. **The role of LH in hypogonadal female infertility patients is clouded by the spectrum of clinical disorders that cause hypogonadotropic hypogonadism with the differing patterns of gonadotropin secretion may further confound clinical outcome results.**

In this reviewer's opinion, the Shoham study (cited above), although limited, also reflects the heterogeneity of hypogonadotropic hypogonadal women in that 33% of these subjects ovulated with FSH alone.⁵

CLINICAL REVIEW

Clinical Review Section

E. Important Issues with Pharmacologically Related Agents

Most adverse events associated with gonadotropin therapy result from ovarian stimulation, follicular development and ovulation. The most concerning serious adverse events are ovarian hyperstimulation syndrome.

Ovarian hyperstimulation syndrome is the least common complication of gonadotropin therapy, but the most serious one. The underlying pathophysiology is unknown, but results in increased vascular permeability. Ovarian hyperstimulation may occur in up to 5% of women that receive gonadotropin therapy.⁶ The treatment for ovarian hyperstimulation syndrome is usually conservative, with management of the increased vascular permeability. Several deaths have been reported from severe ovarian hyperstimulation in the literature.

The overall incidence of ovarian hyperstimulation syndrome using Luveris® in the six clinical studies (6905, 6253, 7798, 8297, 21008 and 21415) for this NDA totals 10 in 152 patients (6.6%). Severe ovarian hyperstimulation in the combined six clinical studies occurred in 3 of 152 patients or approximately 2%.

Reviewer's comment: Of note, Study 21415 reported one patient with severe ovarian hyperstimulation out of 31 patients treated (3%) which is somewhat higher than the usual quoted rate of severe ovarian hyperstimulation of 1-2%.⁷ However, Study 21415 was not powered to compare the rates of ovarian hyperstimulation syndrome.

Since the development of Luveris®, no new trends in adverse events (including ovarian hyperstimulation syndrome) have been identified in this hypogonadal population by the Sponsor or the Division.

F. Foreign Approvals of Luveris®:

There is no indication that Luveris® was withdrawn from the overseas market for any reason. The Sponsor has not reported any actions for safety reasons that were initiated by any regulatory authority or by the Sponsor on Luveris® to date.

G. Other Pharmacologically Related Agents Under Study:

None.

CLINICAL REVIEW

Clinical Review Section

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

Please refer to the pharmacologist's, chemist's and microbiologist's reviews of the original NDA submission for the pertinent findings. Pharmacology considered Luveris® safe for the proposed indication and recommended approval from a pharmacology standpoint. There are no pending approvability CMC or microbiology issues. The tradename Luveris® was reviewed and approved by OPDRA in a memo dated December 17, 2001.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Recombinant-hLH (r-hLH) showed linear pharmacokinetics after IV doses over the 300 to 40,000 IU dose range as assessed by area under the curve. The AUCs are directly proportional to the dose administered.

Additionally, the clearance of Luveris® remains almost constant throughout the studies, with around 5% of the Luveris® dose excreted unchanged in the urine.

B. Pharmacodynamics

The Clinical Pharmacology and Biopharmaceutics Review concluded the following:

- The terminal half-life of 150 IU of r-hLH administered subcutaneously is approximately 14 hours.
- No statistical differences between the intramuscular and subcutaneous routes of administration for C_{max} or bioavailability.
- No pharmacokinetic interaction was been reported between r-hLH and r-hFSH administered simultaneously.

No other drug-drug interaction studies with other r-hFSH formulation have been conducted; raising questions whether combining Luveris® with other marketed r-hFSH products could potentially alter the absorption and/or pK profile of Luveris®. Please refer to the Clinical Pharmacology and Biopharmaceutics Review of NDA 21-322 (finalized October 25, 2001) for further information. Clinical Pharmacology and Biopharmaceutics found the application to be acceptable.

CLINICAL REVIEW

Clinical Review Section

IV. Description of Clinical Data and Sources

A. Overall Data

Previous clinical information:

Five clinical studies (NDA 21-322) were submitted previously to demonstrate efficacy and safety (6905, 6253, 21008, 7798 and 8297). These clinical studies for Luveris® were reviewed in detail (see previous Medical Officer's Review of February 25, 2002). After this initial review, the Division determined that:

- Data in these clinical trials demonstrated no clinically or statistically relevant difference in the efficacy parameters between placebo and Luveris® treatment in these clinical trials.
- The conclusion of a re-assessment of the clinical data by the Medical Officer (dated August 30, 2002) confirmed the need for an appropriately powered, placebo-controlled clinical trial.

The current submission contains the final study report of the additional data from Study 21415 for Luveris®. Study 21415 is a follow-up, single, supportive clinical study conducted by the Sponsor entitled "A phase III, open-label, multi-center study of recombinant human luteinizing hormone (r-hLH) in women with hypogonadotropic hypogonadism and severe LH deficiency to provide continuation of treatment after completing Serono Study 21008." Clinical study 21415 was originally submitted as a synopsis for NDA 21-322. Study 21415 was then submitted as a study report for the NDA (See Amendment N-000-BZ dated April 29, 2003) and as a final study report on May 25, 2004 as part of a complete response to the Non-Approvable Action for Luveris®.

B. Tables Listing the Clinical Trials

The tables for study 21415 are incorporated into this review as Appendix – A. Efficacy Tables for Study 21415 and B. Safety Tables for Study 21415. Additional summaries of the five clinical trials previous submitted are incorporated into this review by cross-reference as Appendix – C. Overview of Completed Clinical Trials for NDA 21-322.

C. Postmarketing Experience

Luveris® is marketed in 52 countries including Denmark, France, Germany, Italy, Sweden, Switzerland and the United Kingdom. From November 2000 through November 2003 there have been approximately 1 of 75 IU sold, and no serious unlabeled events were reported. The Sponsor did not report that any withdrawals or suspensions of the drug had occurred.

CLINICAL REVIEW

Clinical Review Section

Postmarketing Experience (continued):

In the 2001-2002 Annual Report for Luveris® submitted to the IND (#44,108), a total of 42 serious adverse events were reported for IND and non-IND studies with comparable indications. No cases of ovarian hyperstimulation were reported as serious adverse events. Adverse events in subjects in the 2001-2002 Annual Report included:

- 9 premature births
- 4 spontaneous abortions
- 2 ectopic pregnancies
- 2 fetal deaths were reported as an update to Study 21750

The Sponsor reported that there are no ongoing clinical studies at this time.

Reviewer's comment: This worldwide serious adverse event data related to Luveris® is consistent with use of similar gonadotropins for infertility therapy cited in the published literature.

D. Literature Review

Additional publications were obtained from a recent literature search of PubMed that are as references are listed in Appendix - D. References.

V. Clinical Review Methods

A. How the Review was Conducted

This review was conducted from the single supportive follow-up clinical trial (21415), a safety update submitted with the complete response package, an annual report submitted by the Sponsor to IND 44,108, and data from five previous clinical studies submitted to NDA 21-322. In addition, a phase 4 study protocol was reviewed (Appendix – E. Phase 4 Protocol and F. Study Design of Phase 4 Protocol)

B. Overview of Materials Consulted in Review

This application was submitted in paper only. The protocol for Study 21415 was originally submitted to IND 44,108. This review also contains excerpts from the original Clinical Pharmacology and Biopharmaceutics Review dated April 30, 2001, the original Medical Officer's Review dated February 25, 2002, and the Medical Officer's initial review of study 21415 dated September 9, 2003. Clinical trial data from NDA 21-322 was cross-referenced in this review. (see Appendix – C. Overview of Clinical Trials for NDA 21-322). A review of the current published literature on the various pertinent aspects of assisted reproductive technology to date is referred to in an addendum (Appendix – D. References).

CLINICAL REVIEW

Clinical Review Section

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

The submitted clinical trials were previously reviewed (see Medical Officer Reviews for NDA 21-322) and evaluated for data quality. The appropriate DSI audits of four investigators during NDA 21-322 did uncover some inadequacies of protocol violations and record keeping, but these were not considered serious enough to adversely impact on the acceptability of the major studies. Study 21415 is a continuation study of one of the original studies performed (Study 21008), therefore, no additional DSI audits were necessary.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The quality of the informed consent and standard of patient care were previously reviewed for the other clinical studies, and found to be satisfactory during the previous NDA review (see Medical Officer's Review dated February 25, 2002). The Sponsor for Study 21415 submitted a sample informed consent on April 28, 2003. In this reviewer's opinion, the sample informed consent appears acceptable.

E. Evaluation of Financial Disclosure

The financial disclosure statements (FDA 3454) for Luveris® were reviewed previously (see Medical Officer Review of NDA 21-322) and found to be acceptable.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In this reviewer's opinion, Study 21415 is insufficient in design to support efficacy of Luveris® for ovulation induction and pregnancy in this hypogonadal patient population, even in conjunction with previous Phase 3 and Phase 2 clinical trial data presented in the original NDA (21-322). However, this reviewer notes that consideration for approval of this application for Luveris® is based on acceptance by the Division Director that a surrogate endpoint (follicular development) may correlate with the Division's desired endpoint of ongoing pregnancy (as outlined in Subpart H). Completion of the proposed Phase 4 study by the Sponsor will resolve the question of the efficacy of Luveris® in this hypogonadal patient population. The Sponsor has also now agreed to study a dose lower than 75IU as well as the 75IU dose in the Phase 4 study.

CLINICAL REVIEW

Clinical Review Section

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

The Division previously reviewed the efficacy data from studies 6905, 6253, 7798, 8297 and 21008 for Luveris® in the original reviews of NDA 21-322. The Division determined that evidence for efficacy was inadequate to approve Luveris® for concomitant administration along with recombinant human follicle stimulating hormone (r-hFSH) for the induction of ovulation in hypogonadal infertile women with severe LH (< 1.2 IU/L) L deficiency. Study 21415 was an extension of a previous double-blinded, randomized clinical study (21008). Study 21415 was submitted to provide additional clinical data using a surrogate endpoint (follicular development).

C. Detailed Review of Trials by Indication

Study 21415 began in 2000 and ended in 2001.

Study title: "A phase III, open-label, multi-center study of recombinant human Luteinizing Hormone (r-hLH) in women with hypogonadotropic hypogonadism and severe LH deficiency to provide continuation of treatment after completion of study 21008".

Investigator/Location: This study was conducted at 25 centers throughout the United States, Canada, Israel and Australia. These were the same centers that had previously recruited patients for trial 21008 (See NDA 21-322)

Study objective: Study 21415 was designed to provide additional data on follicular development in women with hypogonadotropic hypogonadism and profound luteinizing hormone (LH) deficiency (serum LH less than 1.2 IU/L) and to provide additional safety data on the 75 IU dose of r-hLH administered subcutaneously with FSH in this patient population. Other objectives were to collect additional pregnancy data in this patient population, and to allow women who participated in Study 21008 further opportunity for pregnancy following treatment.

Reviewer's comments: Several issues with the protocol for study 21415 were noted:

1. The protocol for Study 21415 did not prohibit ART procedures such as in vitro fertilization (IVF) and intracytoplasmic injection (ICSI). Study 21415 included one cycle where a patient (#4180004) had ICSI on her second treatment cycle. Patients undergoing ICSI should not be included in studies with ovulation induction patients as the treatment regimen and outcome for patients undergoing intrauterine insemination (IUI) compared to ICSI are different.

CLINICAL REVIEW

Clinical Review Section

Reviewer's comments (continued):

However, exclusion of this patient's second treatment cycle (which did not result in a clinical pregnancy) would not have altered the first cycle treatment, which in this reviewer's opinion, is the critical cycle for evaluation.

- 2. No semen analysis parameters or source of sperm were reported for any of the treated patients. A normal semen analysis was not a requirement for either studies 21008 and 21415. Therefore, it is unknown if inclusion of patients in this study had less male factor infertility than the original study 21008, and essentially enriched this population.**

Study design: Study 21415 was a prospective, open-label, multi-center study to recruit patients who had **previously been treated in Study 21008**, but had not achieved a clinical pregnancy. There was no randomization of patients. A maximum of three treatment cycles were administered. Treatment did not exceed 21 days unless follicle size (≥ 14 mm) indicated imminent follicular maturation.

Patient Population: The final protocol for study 21415 stated that approximately 45 women were expected to be enrolled and treated. A total of 31 eligible patients from 25 participating sites were included in Study 21415; 23 centers enrolled at least one patient. The 31 sites included: 18 US sites, 3 sites in Australia, 1 site in Israel, and 1 site in Canada. The contribution of patients from each site to study 21415 varied from 1 patient ([3.2%] at 15 US sites, 2 Australian sites and the Canadian site) to 3 patients ([9.7%] at the site in Israel, and one in Australia). The subjects were premenopausal women with hypogonadotropic hypogonadism, aged 18 to 39 years old who desired pregnancy. All patients were enrolled from Study 21008, and thus had the same entry requirements, inclusion criteria and exclusion criteria as Study 21008.

Inclusion criteria for entry into Study 21415 were identical to that of Study 21008 including:

- Serum FSH less than 5.0 IU/L
- Serum LH less than 1.2 IU/L
- Serum estradiol level of less than 60 pg/mL.

All patients were re-screened at entry using transvaginal ultrasound to ensure that no new clinically significant uterine or ovarian abnormality had developed since the end of Study 21008. In addition, all patients in Study 21415 had previous history of a negative progesterone challenge test, and were excluded if they had a history of severe ovarian hyperstimulation syndrome.

CLINICAL REVIEW

Clinical Review Section

Patient Demographics: Summary tables of the baseline characteristics and breakdown of primary infertility diagnosis [See Appendix – A. Efficacy Tables 1 and 2], are similar to a previous clinical study for Luveris® (Study 21008 submitted to NDA 21-322) and published studies in hypogonadal women^{5,8}

Reviewer's comment: The percentage of patients with primary amenorrhea (possibly the more severe hypogonadal patients) was clinically equivalent in Study 21415 (52%) compared to the r-hLH treatment arm of Study 21008 (50%).

Patient Disposition: The intent to treat (ITT) group included 31 subjects who were enrolled and treated in the first cycle.

Treatment Protocol: Patients who met the inclusion/exclusion criteria were treated up to three cycles. One vial of r-hLH (75 IU) was to be administered subcutaneously up to 21 days per cycle. The starting daily dose of r-hFSH was either 75 IU or 150 IU, at the discretion of the Investigator, based on the previous cycle. After seven days of treatment, if the patient's response was suboptimal (based on serum estradiol and ultrasound measurements), the dose of r-hFSH could be increased to a maximum of 225 IU. The investigator could decrease the dose of r-hFSH at any time. Patients received their dose administered as either two separate injections of r-hFSH and r-hLH or one combined injection of r-hFSH and r-hLH combined.

Reviewer's comment: Study 21415 allowed the dose of r-hFSH to be based on the patient's response, as opposed to the fixed dose of r-hFSH used in study 21008. This calls into question the results of Study 21415, since there was no appropriate flexible-dose placebo group for comparison.

Primary Efficacy Assessment of Study 21415:

The primary efficacy endpoint designated by the Sponsor was follicular development after three treatment cycles. Follicular development was defined three parameters, all of which had to be met:

- At least one follicle with a mean diameter of ≥ 17 mm on ultrasound
- Preovulatory serum estradiol level of ≥ 109 pg/mL
- Midluteal serum progesterone of ≥ 7.9 ng/mL

Of note, if the patient was discontinued from the study for the risk of ovarian hyperstimulation or was pregnant as determined by serum β -hCG of ≥ 10 mIU/mL, then this patient was considered by the Sponsor as a success for follicular development.

CLINICAL REVIEW

Clinical Review Section

The Sponsor designated multiple secondary efficacy endpoints including:

- Number of follicles ≥ 17 mm on day of hCG
- Serum estradiol level on the day of hCG
- Serum midluteal progesterone level
- Endometrial thickness on day of hCG
- Number of days of gonadotropin treatment
- Patients with biochemical and clinical pregnancies (biochemical pregnancy was defined as a serum hCG level of ≥ 10 IU/L, and clinical pregnancy was defined as fetal sac presence on an ultrasound approximately 35 days after hCG administration)

Reviewer's comments on Sponsor's efficacy endpoints:

1. Study 21415 used a "peak serum estradiol" of ≥ 109 pg/mL and mid-luteal serum progesterone of ≥ 7.9 ng/mL as cut-off levels for "follicular development". More stringently defined minimal (cut-off) levels for serum estradiol and progesterone levels (serum estradiol levels of ≥ 200 pg/mL and serum progesterone levels ≥ 10 ng/mL) to achieve successful follicular development have been supported by the literature. The Division had previously requested that the more stringent serum hormone levels be used to facilitate comparison of the various gonadotropin therapies or that evidence to validate the serum hormone cut-off levels be submitted. To date, the Sponsor has failed to provide adequate documentation in the published literature to validate each efficacy cut-off point for the hormonal values.
2. The results of Study 21415 rely on "peak" serum estradiol level at the time of hCG as being a component of a surrogate endpoint for clinical pregnancy. Serum estradiol values have been accepted as correlating with birth rate⁹ and other secondary endpoints of ovulation induction, including ovarian hyperstimulation rate¹⁰ and multiple pregnancy rate^{11,12}. However, "peak" serum estradiol on the day of hCG is not necessarily predictive of clinical pregnancy outcome.¹³ Therefore, even if the serum estradiol cut-off level chosen by the Sponsor is appropriate, it may not adequately reflect cycle success as either an independent factor or as an addition to the combined endpoint.
3. This reviewer still concludes that patients cancelled for an adverse event (including the risk of ovarian hyperstimulation) should not be counted as a treatment success.
4. In addition, this reviewer has concerns that a positive biochemical test may not reflect ovulation, but residual circulating hCG. Therefore, this reviewer would recommend that if the criteria for follicular development are not met, then success should be confirmed by a clinical pregnancy, and not a biochemical pregnancy.

CLINICAL REVIEW

Clinical Review Section

Reviewer's comments (continued):

5. **The Division currently defines clinical pregnancy as a gestational sac(s) with a fetal heartbeat, in contrast to the Sponsor's definition of only the present of a gestational sac.**

Protocol violations and other allocation issues:

Total allocation – The ITT population was comprised of 31 patients who were treated with at least one dose of medication. These 31 patients could have a maximum of three gonadotropin treatment cycles.

- Eligibility criteria violations: 6 patients (19%) had deviations in eligibility criteria including:
 - 2 patients with lack of informed consent
 - 1 patient with a two week delay in starting treatment
 - 2 patients with delay in obtaining a pre-study evaluation within 6 weeks of completing Study 21008
 - 1 patient that had not completed treatment in accordance with the protocol in Study 21008.
- Treatment violations: 11 patients (35.5%) had deviations during treatment in the intent-to-treat population. (See Appendix –A. Efficacy Table 3)

Reviewer's comment: In this reviewer's opinion, the overall effect of these violations is unknown, but the most concerning is that two patients (#2620001 and 2620002) received r-hLH at a dose of 150-225 IU. This reviewer is concerned whether the optimal dose of r-hLH was identified.

Primary efficacy evaluation for Study MFK/IVF/0399E:

The primary efficacy parameter was based on the follicular development rate. Follicular development was based on the three separate efficacy parameters of estradiol, progesterone and ultrasound criteria, all of which had to be present. The efficacy results of follicular development for Study 21415 are summarized for the ITT population (All patients received follicle stimulating hormone and concomitant administration of 75 IU of Luveris® subcutaneously (See Appendix – A. Efficacy Table 4).

The Sponsor reported that overall "follicular development" rate was:

- 51.6% (16 of 31 patients) in the first cycle for the subjects in the ITT Luveris® treated group [when patients who had treatment cancellation for the risk of ovarian hyperstimulation syndrome (OHSS) were counted as an efficacy failure]
- 63% (34 out of 54 total cycles) in all cycles combined [when patients who had treatment cancellation for the risk of OHSS were counted as an efficacy failure].

CLINICAL REVIEW

Clinical Review Section

Reviewer's comments:

1. In the previous review cycle for this NDA (21-322), the Sponsor has concluded that a patient who was cancelled for risk of OHSS was a success. In this reviewer's opinion, evidence of a physiologic event (indirect evidence of follicular development using ultrasound and serum estradiol levels) may not translate into efficacy.
2. This open-label, non-randomized study did not have a placebo comparison group, and therefore only limited inferences can be made. However, the follicular development and ovulation rates in the first cycle of Study 21415 similarly compares to the follicular development and ovulation rates seen in treatment arm of study 21008 when including patients whose cycles were cancelled for the risk of OHSS are counted as a success (See Appendix – A. Efficacy Table 5).
3. If patients with the risk of OHSS are removed from the success rate, then 21415 has a higher follicular development rate (51%) than the 75 IU r-hLH group in study 21008 (38%), although this difference may not be statistically significant.
4. A difference in follicular development success rates was examined further by reviewing the “gonadotropin naïve” in the first treatment cycle of study 21415 (See Appendix – A. Efficacy Table 6). In these naïve patients, the rate of follicular development (45%) and ovulation (55%) in study 21415 does not appear to be clinically higher than the 75 IU r-LH group treated in study 21008 (follicular development rate of 38% and ovulation rate of 46%), despite flexible dosing. This reviewer theorizes that previous “priming” with treatment of r-hLH in study 21008 (“priming” defined as exposure of the hypothalamic axis to r-hLH (during study 21008) may increase the response of a hypothalamic patient in the follow-up treatment cycle).
5. Treatment failures occurred in 2 patients (#2620003 and #2820001) in the first cycle as they did not meet the criteria for follicular development and did not receive hCG (3.7%). This is lower than seen in the 75 IU r-hLH treatment arm of study 21008 (25%). In this reviewer's opinion, this may represent an improvement in follicular development from the flexible dosing of r-hFSH and/or r-hLH priming.

In this reviewer's opinion, study 21415, the apparent greater rate (compared to that seen in the Phase 3 trial, 21008) of follicular development and ovulation may be result of: 1) flexible FSH dosing or 2) previous exposure to r-hLH [“priming”]. Alternatively, the apparent greater rate of follicular development and ovulation seen in Study 21415 may not represent a real difference since there was no placebo treatment group.

CLINICAL REVIEW

Clinical Review Section

Secondary efficacy endpoints (See Appendix – A. Efficacy Table 4):

The individual hormonal and ultrasound parameters of follicular development (secondary efficacy endpoints) were evaluated separately:

- Serum estradiol (E2) levels on the day of human chorionic gonadotropin (hCG) of ≥ 109 pg/mL was demonstrated in 26 of 31 patients for the first cycle in 21415 (83.9%). A cumulative serum estradiol level of ≥ 109 pg/mL was shown in 46 of 54 total combined cycles (85.2%). **[Reviewer's note: In this reviewer's opinion, the cut-off for E2 should be increased to ≥ 200 pg/mL (a more traditionally used E2 value). Therefore, for the first cycle of Luveris® treatment, the appropriate E2 was demonstrated in 25 of 31 patients in the first cycle of 21415 (80%).]**
- Mid-luteal serum progesterone (P4) level of \geq than 7.9 ng/mL was 18 of 31 patients for the first cycle (58.1%). **[Reviewer's note: However, if the LH naïve patients are used to determine ovulation, the percentage of patients decreases to 54.5% (6 of 11 patients).]**
- The third component of follicular development was ultrasound findings of at least one follicle measuring ≥ 17 mm. This ultrasound finding was documented in 22 of 31 patients on the first treatment cycle (71%). **[Reviewer's note on the use of ultrasound findings as a component of the "follicular development" endpoint: The "follicular development" endpoint includes the number of follicles on ultrasound measuring ≥ 17 mm. It is clear that follicular size reflects the incidence of ovulation¹⁴ and the overall number of mature follicles correlates with improved cycle fecundity.¹⁵ However, questions remain whether ultrasound measurement of follicles is an adequate surrogate endpoint of "follicular development". Other publications have indicated a trend toward higher clinical pregnancy rates with other ultrasound measures as surrogate endpoints for ovulation induction. These include preovulatory follicle numbers¹⁶ and increased vascularity around the follicle¹⁷. Adding to the debate over the correlation of ultrasound measurement of follicles to clinical pregnancy rates is a recent publication that demonstrated that the number of follicles present at the time of intrauterine insemination and the serum estradiol rate at the time of hCG do not affect the clinical pregnancy rate for patients undergoing ovulation induction.¹³ Therefore, although mature follicles on ultrasound may correlate with pregnancy rates, whether these ultrasound findings should be considered an independent surrogate endpoint, or should be used in combination with serum hormonal values is unclear.]**

CLINICAL REVIEW

Clinical Review Section

Reviewer's comments (continued):

In conclusion, the clinical reviewers continue to have concerns about the use of non-standard surrogate endpoints such as "follicular development".

Other secondary efficacy parameters:

- A. The mean endometrial thickness (measured by ultrasound was 9.5 mm with a range of 6.0 mm to 13.2 mm (where patients had ultrasound measurement of the endometrium [n=44 cycles]. The mean measurement in the first cycle was 9.6 mm, and was similar across the three treatment cycles.

Reviewer's comment: Endometrial thickness by itself has been not been correlated with clinical success rates in a recent uncontrolled clinical studies of ovulation induction cycles.¹⁸ Endometrial measurements and wave-forms documented by ultrasound are still considered a research tool.

- B. The clinical pregnancy rate for 75 IU of Luveris® when administered in Study 21415 was 16 clinical pregnancies in 54 total cycles (29.6% pregnancy rate per cycle). All clinical pregnancies occurred in the first two treatment cycles (See Appendix – A. Efficacy Table 7).

Reviewer's comment: It is unknown why Study 21415 had a higher pregnancy rate than the r-hLH treatment arm of Study 21008, but there were far too few clinical pregnancies in Study 21008 to make any comparisons (See Appendix – A. Efficacy Table 5). In addition, this reviewer notes that patient cancellation for the risk of ovarian hyperstimulation syndrome was much lower in study 21415 for both gonadotropin naïve and the overall patient population as compared to study 21008 (See Appendix – A. Efficacy Tables 5 and 6), despite having identical criteria for cancellation in both studies. This reviewer has concerns that the flexible dosing may allow more patients to achieve follicular development rather than cancellation, and therefore pregnancy. Therefore, in this reviewer's opinion, a conclusive study to confirm whether the flexible r-hFSH dosing was responsible for the improved pregnancy rate in 21415 is necessary.

- C. The average daily dose of r-hFSH was noted to be ≥ 150 IU in a majority of treatment cycles (38 cycles of 54 total cycles [70%]) and < 150 IU in 16 of the 54 total treatment cycles [30%]).

Reviewer's comments: It is interesting that most patients in Study 21415 (70%) required more than the 150 IU of r-hFSH. In the Phase 3 Study 21008, a fixed FSH dose of 150 IU was used.

CLINICAL REVIEW

Clinical Review Section

Reviewer's comments (continued):

This reviewer does **not** conclude that less patients were cancelled for the risk of OHSS on when placed on 150 IU or higher dose of r-hFSH in Study 21415 (5 patients in 38 cycles [10%]) when compared to patients on fixed doses of 150 IU r-hFSH plus 75 IU r-hLH in Study 21008 (5 patients in 24 cycles [20.8%]). The apparent differences most likely reflect the smaller number of cycles in 21008 compared to 21415. However, it is unclear whether the addition of LH may not necessarily improve the outcome of treatment in these hypogonadal patients. The possibility an "LH threshold", above which LH may be detrimental to cycle control, has been suggested in a recent study that suggests that only when serum LH was suppressed to < 1 IU/L did exogenous LH increase the number of developmentally competent oocytes.¹⁹ In conclusion, this reviewer continues to have significant concerns that the efficacy data in Study 21415 does not meet the requirements of a "pivotal" study as recommended by the Division. This conclusion is based on:

- Study 21415 did not have an appropriate placebo treatment arm to compare to Luveris® at the 75 IU dose, a new clinical trial should include a placebo treatment arm. This will allow "treatment failures" defined as a failure to respond, to be adequately assessed in the context of comparison with placebo.
- The results of Study 21415 hinge on the inclusion of patients cancelled for the risk ovarian hyperstimulation syndrome. These cancellations continues to be a clinical concern with Luveris®. The rates of these "failures" at the proposed dose of Luveris® (75 IU) support the need for additional clinical trials.
- Open-label, non-blinded trials are not acceptable for the purpose of obtaining "pivotal" efficacy information. An appropriate randomized, double-blind dose finding trial would be necessary to prove efficacy claims such as proposed in the phase 4 study.

Appears This Way
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CLINICAL REVIEW

Clinical Review Section

D. Efficacy Conclusions

In this reviewer's opinion, Study 21415 is not adequate to support the efficacy of Luveris® in this hypogonadal patient population, and does not address the two clinical issues raised in the Non-Approvable Action. This small, open-label, follow-up clinical trial (Study 21415):

- 1. constituted the second treatment cycle for patients recruited from a previous study (21008). Re-recruiting hypogonadal patients precludes statistical comparison with other previous initial clinical studies (21008, 6253, and 6905).**
- 2. provided an inadequate number of LH naïve patients. The small numbers of patients in Study 21415 resulted in the study being underpowered to reach statistical conclusions.**
- 3. demonstrated a lack of efficacy in over a third of patients by the Division's analysis.**
- 4. has not resolved the question of the lowest effective dose for Luveris® in this patient population.**
- 5. does not have another dose comparison group**

Therefore, Study 21415 does not support the results of either Study 6905 or Studies 21008 and 6253, and does not provide additional evidence to determine the patient population that would most benefit from Luveris® treatment. Furthermore, Study 21415 continues to raise questions about a Luveris® regarding lack of efficacy with respect to ovulation and clinical pregnancy in a significant number of hypogonadal patients.

To answer the question of efficacy, the Sponsor's proposed phase 4 study (See Appendix – E. Phase 4 Protocol Outline) will provide the additional data necessary to determine whether LH truly demonstrates efficacy in this severely hypogonadal population. However, this reviewer notes that the minimum required dose for the hypogonadal population in the United States is still unknown. To answer this question, an additional dose-finding study would be necessary.

CLINICAL REVIEW

Clinical Review Section

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Safety of Luveris® was primarily derived from:

1. Previously submitted clinical data acquired from the trials previously reviewed in NDA 21-322.
2. A supportive trial that was submitted (Study 21415)
3. A Safety Update submitted July 19, 2004

The safety data does not appear to demonstrate evidence of new clinical safety issues with Luveris®. This reviewer concurs with the original Medical Office's Reviewer's conclusion that there are no major safety issues to resolve with Luveris®. The Sponsor should submit safety data from the phase 4 study to the Agency for consideration when the study is completed.

B. Description of Patient Exposure

Completed clinical trials using Luveris® (previous trade name LHadi) include 5 previously submitted clinical trials (6253, 6905, 7798, 8297, and 21008) and the current submitted extension Study 21415. Patient exposure is adequate and the safety profile for Luveris® is anticipated to be similar to other gonadotropin products.

C. Methods and Specific Findings of Safety Review

The safety data for Luveris® is based on:

- Data from the studies previously reviewed in the original NDA (21-322) for Luveris®. (See Medical Officer's original review of Luveris® (NDA 21-322) dated February 25, 2002).
- Data from clinical study 21415 (an extension of study 21008).
- Data from a Safety Update dated July 19, 2004.

Safety Review of Study 21415:

Patient Disposition/Treatment: The evaluable group assessed for safety included 31 patients who were enrolled and treated with gonadotropin for a total of 54 cycles. Adverse events were coded using the WHO Adverse Event Reaction Terminology Dictionary, and the severity of adverse events was graded by the Investigator.

CLINICAL REVIEW

Clinical Review Section

The safety assessments reported by the Sponsor for Study 21415 included:

- Overall adverse events
- Serious adverse events
- Ovarian hyperstimulation syndrome
- Laboratory safety data
- Multiple pregnancy rate
- Study termination rate

1. Overall Adverse Events:

In the supportive clinical trial (Study 21415), there were 65 adverse events in 15 subjects who had a total of 54 treatment cycles. The Sponsor reported that most of these adverse events were mild or moderate. Adverse events that were most frequently reported by patients in the treatment groups were flatulence (16%) and headache (9.7%) (See Appendix – B. Safety Table 1).

2. Serious Adverse Events:

There were no patient deaths or thromboembolic adverse events during Study 21415. There was one serious adverse event (3.2%) – a patient with severe ovarian hyperstimulation syndrome in one patient).

- Luveris® treated subject #4170001, who was noted to be pregnant following the induction protocol, developed severe ovarian hyperstimulation required hospitalization for six days. The patient received IV fluids and bedrest during her hospital stay, recovered, and subsequently delivered a livebirth.

Reviewer's comments on adverse event rates:

1. **It is difficult to compare Study 21415 to previous studies of Luveris® that used a fixed dose of FSH. However, since the patient population of 21008 and 21415 are essentially similar, a review of the most common adverse events in Study 21415 does not appear clinically different in absolute number of adverse events or occurrence of serious adverse events from the 75 IU arm of Luveris® in Study 21008. (see Appendix – B. Safety Table 1).**
2. **The occurrence of ovarian hyperstimulation (both overall and severe) appears to be similar to a previous trial with Luveris® (see Appendix – B. Safety Table 1) and to other published gonadotropin clinical trials.^{6,7}**

CLINICAL REVIEW

Clinical Review Section

3. Multiple pregnancies:

Multiple pregnancies were noted in 6 of 16 pregnancies in Study 21415 (a multiple birth rate of 11% per cycle). Five subjects delivered twins, one subject had triplets, and two patients had fetal reductions. There were sixteen patients with clinical pregnancies and four patients that had “chemical pregnancies”.

Reviewer’s comment: Study 21415 was not powered to determine the incidence of multiple pregnancy rates for Luveris®. However, this data is consistent with a published multiple pregnancy rates for women with hypothalamic amenorrhea treated with pulsatile gonadotropin-releasing hormone of 12%.⁸

4. Laboratory Safety Data:

Patients were evaluated for clinical laboratory parameters (hematology, blood chemistry and urinalysis) at baseline (for most patients these values were obtained post-study 21008) and post-study 21415. All clinical laboratory assessments were performed at a central laboratory.

a. Hematology:

The routine hematology parameters included: hematocrit, neutrophils and white blood cell count. No clinically significant differences in median hemoglobin, hematocrit or white blood cell count were seen between the baseline and post-treatment levels.

Clinically significant individual hematology laboratories seen post-treatment:

- Platelet – Two patients (#0480001 and 4340002) had elevated platelets post-study (403,000 and 464,000 per cumm - upper limit of normal 400,000 per cumm).
- White blood count – One patient (# 4360001) had an elevated white blood cell count post-study (12.4 thousand/MCL – upper limit of normal 10.8 thousand per MCL). Post-study, this patient was found to have a clinical pregnancy.

Reviewer’s comment: The most concerning individual hematology values were noted in patient #3920005 who had thalassemia. This patient was noted to have a low hemoglobin and hematocrit (8.4 g/dL and 26.0 %, respectively) and a high platelet count (511,000 per cumm) post-study. In this reviewer’s opinion, the abnormalities were probably secondary to thalassemia, although it is unfortunate that no pre-study laboratories were drawn. No other clinically significant changes in hematology values from baseline to post-treatment were seen and there did not appear to be any other individual hematology values or trends of concern.

CLINICAL REVIEW

Clinical Review Section

Laboratory Safety Data (continued):

b. Chemistry:

The routine chemistry parameters included: sodium potassium, chloride, glucose, calcium, BUN, Creatinine, total bilirubin, total protein, AST and ALT. No clinically significant differences in any of the median chemistry values were seen between the baseline and post-treatment levels.

Clinically significant individual chemistry laboratories seen post-treatment:

- Glucose – One patient (#5250003) shifted from a normal blood glucose to a glucose of 176 mg/dL [upper limit of normal 115 mg/dL]
- Chloride – One patient (#5430002) shifted from a normal blood chloride to a chloride of 111 meq/L from a normal value [upper limit of normal 108 meq/L.]

Reviewer's comment: No other clinically significant changes in chemistry values from baseline to post-treatment were seen. In addition, there did not appear to be any other individual chemistry values or trends of concern. However, this reviewer notes that the safety data in Study 21415 was extremely limited, (only 22 patients had hematology values, and 23 had blood chemistry values of the 31 treated patients), which makes it difficult to reach conclusions.

5. Study termination for Study 21415:

Treatment with FSH and Luvris® and/or human chorionic gonadotropin (hCG) were withheld for any of the following reasons (i.e. study termination):

- Serious adverse event that is drug related
- Pregnancy
- Treatment failure
- Risk of ovarian hyperstimulation syndrome (OHSS)
- Protocol violations, including non-compliance and lost to follow-up
- Serious intercurrent illness or worsening of intercurrent illness
- Adverse events
- Administrative reasons

No patient in this study cancelled because of an actual adverse event.

Reviewer's comments: The major cancellation rate of safety concern is cancellation for risk of OHSS. The Sponsor noted that 5 patients in the first cycle (16%) were cancelled for this risk (although no patients in cycles 2 or 3 were cancelled).

CLINICAL REVIEW

Clinical Review Section

Reviewer's comments (Continued): This reviewer considers the cancellation rate clinically higher than seen in a previous large OI study (approximately an overall 4% cycle cancellation rate in Study 22240 in NDA 21-765 in WHO Group II anovulatory patients using a recombinant FSH). This reviewer does note that the estradiol value defined in the protocol that resulted in cancellation in Study 21415 was 1,100 pg/mL, which is somewhat lower than that usually used in clinical practice, and may have led to an increased cancellation rate for risk and a lower rate of actual ovarian hyperstimulation syndrome (1 patient - 3.2%). This study appears to have a similar cancellation rate for the risk of OHSS to the fixed FSH dose ovulation induction study for Luveris® (Study 21008 with a cycle cancellation rate in the 75 IU Luveris® arm of 20.8%). It is noted that the criteria for cancellation for the risk of OHSS were identical in both Studies 21008 and 21415. Therefore, completion of the phase 4 study (using a higher estradiol cut-off level for cancellation for the risk of OHSS than Studies 21008 and 21415) will be crucial in determining if Luveris® alters the rate of clinically significant OHSS, as the rate of cycle cancellation for the risk of ovarian hyperstimulation should decrease.

Safety Review of Submitted Safety Update:

The Safety Update reported by the Sponsor included 3100 patients in 41 clinical studies who were exposed to a total of 20,504,754 IU of r-hLH with a mean patient exposure of 6,614 IU. No deaths were reported in any of the 41 clinical studies. The Integrated Summary of Safety included:

- Overall adverse events for the six clinical studies submitted to NDA 21-322 (6905, 6253, 21008, 8297, 7798 and 21415).
- Ovarian hyperstimulation syndrome for all six clinical studies submitted to NDA 21-322 (6905, 6253, 21008, 8297, 7798 and 21415).
- Pregnancy Outcomes in the six clinical studies submitted to NDA 21-322 (6905, 6253, 21008, 8297, 7798 and 21415).

The Sponsor also reported that:

- There were no reports of clinically significant laboratory abnormalities for any of the blood chemistry, hematology and urinalysis parameters assessed in the six clinical studies submitted to the NDA.
- In the 52 countries in which Luveris® has been approved, no serious unlabeled adverse events have been reported.

In addition, the Sponsor included a report of all Serious Adverse Events for all patients in all 41 clinical studies that treated patients with r-hLH.

CLINICAL REVIEW

Clinical Review Section

Safety Review of Submitted Safety Update (continued):

1. Overall Adverse Events for the six submitted clinical studies submitted to the NDA (6905, 6253, 7798, 8297, 21008 and 21415):

There were 212 adverse events reported in the 152 patients treated in the six clinical studies. The Sponsor reported that most of these adverse events were mild or moderate. Adverse events that were most frequently reported by patients in the treatment groups were headache in 15 patients (9.9%) and abdominal pain in 13 patients (8.6%) (See Appendix – B. Safety Table 2).

Reviewer's comment: No new trends were noted in this data.

2. Ovarian Hyperstimulation Syndrome in the six submitted clinical studies (6905, 6253, 7798, 8297, 21008 and 21415):

Across all studies and all cycles for the six submitted clinical studies for NDA 21-322, 10 patients (6.6%) reported Ovarian Hyperstimulation Syndrome in 152 patients treated with r-hLH. There were 2 cases of severe OHSS in patients treated with r-hLH (1.3%).

3. Pregnancy Outcomes Syndrome in the six submitted clinical studies (6905, 6253, 7798, 8297, 21008 and 21415):

In all studies and all cycles for the six submitted clinical studies for NDA 21-322, there were 173 patients treated with r-hLH who were willing to conceive who had a total of 259 treatment cycles. The Sponsor noted:

- 50 clinical pregnancies (19% pregnancy rate per cycle)
- 40 livebirths (15% livebirth rate per cycle)
- 16 multiple pregnancies of twins or greater (6% multiple pregnancy rate per cycle)

The Sponsor reported 112 Serious Adverse Event reports for all 3100 patients who received r-hLH. There were no patient deaths or thromboembolic adverse events noted. The most common Serious Adverse Events in all patients reported in r-hLH treatment groups included ovarian hyperstimulation syndrome in 19 treated patients and ectopic pregnancy in 17 treated patients. The Sponsor also reported available obstetric outcomes including:

- 10 premature deliveries
- 2 in utero deaths
- 2 infants with Trisomy 21

Reviewer's comment: No concerning trends in adverse events, ovarian hyperstimulation syndrome, pregnancy outcomes or postmarketing data although these studies were not powered to show differences in these safety endpoints.

CLINICAL REVIEW

Clinical Review Section

D. Adequacy of Safety Testing

Safety data has been collected since the original clinical trials for Luveris® began in 1993. Patient exposure has been adequately documented from a safety perspective, although continued monitoring of the safety profile will be necessary given the small numbers of patients in the clinical trials.

E. Summary of Critical Safety Findings and Limitations of Data

The safety update from the Sponsor was submitted in the complete response, and included data from the six clinical studies submitted to the NDA (6253, 6905, 8297, 7798, 21008 and 21415). The Sponsor notes that:

- No deaths or thromboembolic events were reported by the Sponsor during any of the clinical trials submitted to this NDA.
- The most common adverse events noted in r-hLH treated patients (combining all six clinical studies above) were: headache (15 patients [9.9%]) and abdominal pain (13 patients [8.6%])

Reviewer's comments:

1. The safety database (although small) supports the previous Medical Officer's comments that, from a clinical safety perspective, approval of this product is acceptable.
2. It is difficult to assess the effect of Luveris® on the rate of ovarian hyperstimulation syndrome (OHSS), since the safety data is sparse and the post-marketing information may not be uniform in reporting the severity. The OHSS adverse event rate reported for Luveris® (3.8%) appears to be lower than a recently submitted ovulation induction study (NDA 21-765 – Study 22240) of 6.5%. However, the rate of ovarian hyperstimulation cases may be lower as a result of a higher cycle cancellation rate (16% - for the risk of ovarian hyperstimulation syndrome). The proposed phase 4 protocol increased the estradiol cut-off value for cycle cancellation (for the risk of ovarian hyperstimulation) to 2000 pg/mL. Although this reviewer notes that the proposed estradiol cut-off in the phase 4 study is lower than American Society of Reproductive Medicine's suggested estradiol cut-off level of 2,500 pg/mL.²⁰ Therefore, the phase 4 study will be necessary not only to evaluate efficacy, but to examine the true rate of ovarian hyperstimulation syndrome with use of Luveris®.

CLINICAL REVIEW

Clinical Review Section

VIII. Dosing, Regimen, and Administration Issues

The dosing presented in Study 21415 for Luveris® is identical to that of Study 21008 (see submitted NDA 21-322). Patients in Study 21415 received one vial of r-hLH of 75 IU administered subcutaneously with concomitant recombinant follitropin alfa throughout the treatment cycle for up to 21 days per cycle.

Reviewer's comments:

1. **This open-label extension study (21415) of study 21008 used a daily dose of 75 IU r-hLH for all patients. Therefore, Study 21415 does not provide additional data to determine the lowest effective dose of LH required in this patient population.**
2. **Another concern with study 21415 is the question of whether r-hFSH and r-hLH should be administered concomitantly or separately. Study 21415 had 16 cycles where 9 patients used a combined single injection of r-hFSH and r-hLH and 37 cycles where 22 patients used separate injections of r-hFSH and r-LH. This reviewer notes that Study 21415 was not powered to differentiate whether significant differences in efficacy could occur when gonadotropins are mixed and used concomitantly. However, the majority of cycles in Study 21415 and all patients in Study 21008 were given as two separate injections. Therefore, this reviewer recommends that the instructions for administration should be identical to study 21008.**

The Sponsor's Complete Response (dated May 25, 2004) to the Division's Approvable Action (dated April 30, 2004) included a revised label based on the information from study 21415. The Division and the Sponsor negotiated the label through correspondence between May 25 and September 8, 2004. The Sponsor's version of the label (dated September 8, 2004) was accepted by the Division Director on September 28, 2004 although the label is not finalized at this date and therefore is not attached to this review. The final label will be attached in the Approval letter.

Reviewer's comments on final label:

1. **This reviewer does not concur with the decision to include the efficacy results of Study 21415 in the label. In this reviewer's opinion, information from an uncontrolled, non-randomized study is not helpful to the practitioner.**
2. **In addition, this reviewer does not concur with the decision to include secondary efficacy endpoints (pre-ovulatory serum estradiol and endometrial thickness) in the label. In this reviewer's opinion, studies 6253 and 21008 were not powered to demonstrate these endpoints, and therefore this information is misleading.**

CLINICAL REVIEW

Clinical Review Section

Reviewer's comments on the label (continued):

3. **The reviewer also noted that the measurement of endometrial thickness was not controlled or calibrated by center, and is therefore, a non-validated experimental endpoint.**

IX. Use in Special Populations

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

Treatment using Luveris® is being approved for hypogonadal patients to use for ovulation induction in women only.

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

Clinical studies of Luveris® did not include patients aged 65 and over. Use of Luveris® is contraindicated in pregnancy. It is not anticipated that race or ethnicity would make a difference in the efficacy of the drug.

C. Evaluation of Pediatric Program

Luveris® is not indicated for use in pediatric populations and safety and efficacy in such patients have not been established.

X. Conclusions and Recommendations

A. Conclusions

This reviewer concurs with the previous Medical Officer Review dated February 25, 2002 that the Sponsor has not substantiated the clinical efficacy of Luveris®. However, a decision was made by the Division Director that this application met the requirements for approval under sub-part H and that the efficacy of Luveris® could be inferred using a surrogate endpoint of follicular development. The proposed phase 4 protocol should provide definitive evidence regarding the efficacy of Luveris®.

CLINICAL REVIEW

Clinical Review Section

B. Recommendations

1. The risk/benefit ratio of using Luveris® is unclear at this time. Furthermore, there may be outstanding issues with co-administration of r-hLH and other r-hFSH drug products that have not been identified.
2. It is recommended that the phase IV study proceed, and the final determination of benefit be reassessed when the study is completed.
3. The Sponsor should receive the Medical Reviewer's comments (#1 through #13) in Appendix – E. Phase 4 Protocol Outlines and an amended safety update with additional safety data as described above should be sent to the Division.

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CLINICAL REVIEW

Clinical Review Section

Appendix

A. Efficacy Tables from Study 21415

Table 1: Demographics of Studies 21415 and 21008

	Study 21415	Study 21008
N	N=31	N=39
Primary Amenorrhea	16 (51%)	19 (56%)
Secondary Amenorrhea	15 (48%)	15 (44%)
Primary Infertility	25 (80%)	27 (74%)
Secondary Infertility	6 (19%)	7 (21%)
Parity		
0	28 (90%)	29 (85%)
1	2 (6.3%)	4 (12%)
2	1 (3.2%)	1 (2.9%)
Duration of infertility (Months)		
Mean (SD)	38.8 (36.9)	35.9 (33.2)

Table 2 – Primary Infertility Diagnosis Breakdown of Studies 21415 and 21008

Primary diagnosis	Study 21415	Study 21008
N (completed study)	N=31	N=39
Hypothyroidism	3 (10%)	3 (7%)
Hypothalamic Amenorrhea	2 (6%)	2 (5%)
Kallman's Syndrome	4 (13%)	3 (7.7%) (1 withdrew)
Panhypopituitarism	1 (3%)	1 (3%)

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On Original

CLINICAL REVIEW

Clinical Review Section

Appendix

Efficacy Tables (continued)

Table 3: Treatment Violations

Patient Number	Violation(s)
1270002	Missed one day of r-hFSH treatment Missed on day of r-hLH treatment
4150001	Missed one day of r-hFSH treatment Missed three doses of r-hLH treatment Started at a higher dose of r-hFSH than was specified in the protocol (225 IU)
4170001	Missed one day of r-hFSH treatment Missed one day of r-hLH treatment
2820001	Missed one day of r-hLH treatment
3920005	Missed one day of r-hLH treatment Exceeded maximum FSH dose of 225 IU (300-375 IU) Treated for greater than 21 days
2530002	Received dose of r-hFSH lower than specified 75 IU (37.5) and received FSH on day of hCG
2620001	Received r-hLH at a dose of 150-225 IU Exceeded maximum FSH dose of 225 IU(300 IU)
2620002	Received r-hLH at dose of 150-225 IU
2820001	Exceeded maximum FSH dose for one day (450 IU)
4180002	Treated for greater than 21 days
4180004	Started at a higher dose of r-hFSH than was specified in the protocol (225 IU)

Appears This Way
On Original

CLINICAL REVIEW

Clinical Review Section

Appendix

Efficacy Tables (continued)

Table 4: ITT Patients in the three treatment cycles of 21415

	Study 21415 75 IU r- hLH (1 st cycle n=31)	Study 21415 75 IU r- hLH (2 nd cycle n=15)	Study 21415 75 IU r- hLH (3 rd cycle n=8)
Primary Efficacy Variable: Protocol Definition: OHSS=success Follicular Development			
Success (%)	21 (67.7%)	12(80%)	6(75%)
Failure (%)	10 (32.3%)	3(20%)	2(25%)
Primary Efficacy Variable: Reclassify OHSS=failure Follicular Development			
Success (%)	16 (51.6%)	12(80%)	6(75%)
Failure (%)	15 (48.4%)	3(20%)	2(25%)
Secondary Efficacy Variables:			
Follicle Size:			
At Least One Follicle \geq 17 mm			
Success (%)	26 (83.9%)	14(93%)	8(100%)
Failure (%)	5 (16.1%)	1(6.7%)	0(0%)
Pre-Ovulatory E ₂ Level \geq 109 pg/mL			
Success (%)	26 (83.9%)	12(80%)	8(100%)
Failure (%)	5 (16.1%)	3(20%)	0(0%)
Mid-Luteal P ₄ Level \geq 7.9 ng/mL			
Success (%)	18 (58.1%)	11(73%)	6(75%)
Failure (%)	13 (41.9%)	4(27%)	2(25%)
Clinical Pregnancy			
Success (%)	11(35.5%)	5 (33.3)	0(0%)
Failure (%)	20(64.5%)	10(66.7)	8(100%)
Risk of OHSS			
Yes (%)	5(16.1%)	0(0%)	0(0%)
No (%)	26(83.9%)	15(100%)	8(100%)
Endometrial Thickness (mm)			
Mean (S.D.)	9.6(1.4)	9.3(1.7)	9.7(1.1)

CLINICAL REVIEW

Clinical Review Section

Appendix

Efficacy Tables (continued)

Table 5: ITT Patients comparing overall studies #21415 and 21008)

	Study 21415 75 IU r-hLH (1 st cycle n=31)	Study 21008 Placebo (n=13)	Study 21008 75 IU r-hLH (n=26)
Primary Efficacy Variable: Protocol Definition: OHSS=success Follicular Development Success (%) Failure (%)	21 (67.7%) 10 (32.3%)	2 (15%) 11 (85%)	16 (62%) 10 (38%)
Primary Efficacy Variable: Reclassify OHSS=failure Follicular Development Success (%) Failure (%)	16 (51.6%) 15 (48.4%)	1 (8%) 12 (92%)	10 (38%) 16 (62%)
Secondary Efficacy Variables:			
Follicle Size: At Least One Follicle \geq 17 mm Success (%) Failure (%)	26 (83.9%) 5 (16.1%)	4 (31%) 9 (69%)	16 (62%) 10 (38%)
Pre-Ovulatory E₂ Level \geq 109 pg/mL Success (%) Failure (%)	26 (83.9%) 5 (16.1%)	2 (15%) 11 (85%)	16 (62%) 10 (38%)
Mid-Luteal P₄ Level \geq 7.9 ng/mL Success (%) Failure (%)	18 (58.1%) 13 (41.9%)	2 (15%) 11 (85%)	12 (46%) 14 (54%)
Clinical Pregnancy Success (%) Failure (%)	11(35.5%) 20(64.5%)	1 (8%) 12 (92%)	1 (4%) 25 (96%)
Risk of OHSS Yes (%) No (%)	5(16.1%) 26(83.9%)	1 (8%) 12 (92%)	6 (23%) 20 (77%)
Endometrial thickness (mm) Mean (S.D.)	9.6(1.4)	4.1(2.9)	6.7(3.2)

CLINICAL REVIEW

Clinical Review Section

Appendix

Efficacy Tables (continued)

Table 6: ITT Patients in 1st treatment cycle of 21415 (only gonadotropin naïve patients) compared to Study #21008

	Study 21415 naïve patients (n=11)	Placebo (n=13)	75 IU r-hLH (n=26)
Primary Efficacy Variable:			
Protocol Definition: OHSS=success			
Follicular Development			
Success (%)	7(64%)	2 (15%)	16 (62%)
Failure (%)	4(36%)	11 (85%)	10 (38%)
p-value vs. placebo (Fisher's Exact Test)			
Primary Efficacy Variable:			
Reclassify OHSS=failure			
Follicular Development			
Success (%)	5(45%)	1 (8%)	10 (38%)
Failure (%)	6(55%)	12 (92%)	16 (62%)
p-value vs. placebo (Fisher's Exact Test)			
Secondary Efficacy Variables:			
Follicle Size:			
At Least One Follicle \geq 17 mm			
Success (%)	8(73%)	4 (31%)	16 (62%)
Failure (%)	3(27%)	9 (69%)	10 (38%)
p-value vs. placebo (Fisher's Exact Test)			
Pre-Ovulatory E ₂ Level \geq 109 pg/mL			
Success (%)	8(73%)	2 (15%)	16 (62%)
Failure (%)	3(27%)	11 (85%)	10 (38%)
p-value vs. placebo (Fisher's Exact Test)			
Mid-Luteal P ₄ Level \geq 7.9 ng/mL			
Success (%)	6(55%)	2 (15%)	12 (46%)
Failure (%)	5(45%)	11 (85%)	14 (54%)
p-value vs. placebo (Fisher's Exact Test)			
Clinical Pregnancy			
N (patients who desired pregnancy)	11	1 (8%)	1 (4%)
Success (%)	4 (36%)	12 (92%)	25 (96%)
Failure (%)	7 (64%)		
p-value vs. placebo (Fisher's Exact Test)			
Risk of OHSS			
Yes (%)	1 (9%)	1 (8%)	6 (23%)
No (%)	10 (91%)	12 (92%)	20 (77%)
p-value vs. placebo (Fisher's Exact Test)			

CLINICAL REVIEW

Clinical Review Section

Appendix

Efficacy Tables (continued)

Table 7: Pregnancy Breakdown for Study 21415 by Amenorrhea Status

Amenorrhea	Cycle 1	Cycle 2	Total
Primary	6 clinical pregnancies (6 of 16 patients)	2 clinical pregnancies	8 clinical pregnancies in primary group
Secondary	5 clinical pregnancies (5 of 15 patients)	3 clinical pregnancies	8 clinical pregnancies in secondary group
Total	11 pregnancies	5 clinical pregnancies	16 total clinical pregnancies in 54 total cycles (29.6% per cycle)

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On Original

CLINICAL REVIEW

Clinical Review Section

Appendix

B. Safety Table from Study 21415:

Table 1: Comparison of patient adverse events in Study 21415 compared to previous clinical trial (21008).

WHO dictionary preferred term	Study 21415 -- 75 IU Luveris® (All treated patients in all cycles) n*(n%)	Study 21008 -- 75 IU Luveris® group n*(n%)
Total patient number	n = 31	n=27
Abdominal Pain	2 (6.5%)	4 (14.8%)
Breast Pain	2 (6.5%)	0
Flatulence	5 (16.1%)	1 (3.7%)
Headache	3 (9.7%)	4 (14.8%)
Injection site inflammation/bruising	2 (6.5%)	2 (7.4%)
Nausea	2 (6.5%)	2 (7.4%)
Ovarian Cyst*	1 (3.2%)	1 (3.7%)
Ovarian Hyperstimulation	1 (3.2%)	0

n* - number of patients

Appears This Way
On Original

CLINICAL REVIEW

Clinical Review Section

B. Safety Table from Safety Update for NDA 21-322 (Studies 6905, 6253, 7798, 8297, 21008 and 21415):

Table 2: Safety Update Adverse Event Rates

WHO dictionary preferred term	All r-hLH treated patients n*(n%)
Total patient number	n=152
Abdominal Pain	13 (8.6%)
Breast Pain	9 (5.9%)
Flatulence	3 (2.0%)
Headache	15 (9.9%)
Injection site reaction	6 (3.9%)
Nausea	11 (7.2%)
Ovarian Cyst	8 (5.3%)
Ovarian Hyperstimulation	9 (5.9%)

n* - number of patients

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On Original

CLINICAL REVIEW

Clinical Review Section

Appendix

C. Overview of Completed Clinical Trials for NDA 21-322

1. Study 6905 – An open-label, placebo-controlled, randomized, parallel arm, multi-center trial in the United States that included forty patients with serum LH levels less than 13.3 IU/L were entered into the trial and could receive up to three cycles of therapy. Patients were recruited from 14 sites only randomized to first cycle, however, only the first cycle is considered primary for efficacy. Luveris® treatment was with 0, 25, 75 and 225 IU doses.

Analysis of success for follicular development (6905)	Placebo	Luveris® 25 IU	Luveris® 75 IU	Luveris® 225 IU	p-value
Sponsor's (Evaluable) %	64%	100%	73%	67%	0.774 (Trend test)
Division's re-analysis(ITT)* %	45%	78%	64%	67%	0.670 (Fisher's)**

*As opposed to the Sponsor, the Division excluded all subjects from analysis that had a risk of ovarian hyperstimulation. These subjects who did not complete treatment cycles were considered failures.

** Fisher's test performed comparing 75 IU versus placebo.

2. Study 6253 – An open-label, placebo-controlled, randomized, parallel arm, multi-center trial in Europe and Israel that included thirty-eight patients with serum LH of less than 1.2 IU/L were entered into the trial and could receive up to three cycles of therapy. Patients were recruited from 10 sites only randomized to first cycle, however, only the first cycle is considered primary for efficacy. Treatment was with 0, 25, 75 and 225 IU doses of Luveris®.

Analysis of success of follicular development (6253)	Placebo	Luveris® 25 IU	Luveris® 75 IU	Luveris® 225 IU	p-value
Sponsor's (Evaluable) %	11%	25%	64%	70%	0.004 (Trend test)
Division's re-analysis (ITT)* %	11%	25%	45%	40%	0.157 (Fisher's)**

*As opposed to the Sponsor, the Division excluded all subjects from analysis that had a risk of ovarian hyperstimulation. These subjects who did not complete treatment cycles were considered failures.

** Fisher's test performed comparing 75 IU versus placebo.

CLINICAL REVIEW

Clinical Review Section

Appendix

C. Overview of Completed Clinical Trials for NDA 21-322 (Continued):

3. Study 7798 – An open-label, randomized, dose-finding, cross-over multi-center trial in Germany that included fifteen patients with serum LH of less than 1.2 IU/L were entered into the trial and could receive up to three cycles of therapy. Patients were recruited from seven sites and randomized to a random treatment sequence. However, only the first cycle of treatment is considered primary for efficacy. Treatment was with 75, 150 and 225 IU doses of Luveris® in a random order.

Analysis of success of follicular development (7798)	Luveris® 75 IU	Luveris® 150 IU	Luveris® 225 IU	p-value
Sponsor's (Evaluable) %	40%	20%	60%	N/A**
Division's re-analysis (ITT)* %	20%	0%	40%	N/A**

*As opposed to the Sponsor, the Division excluded all subjects from analysis that had a risk of ovarian hyperstimulation. These subjects who did not complete treatment cycles were considered failures.

**This is a small exploratory study, and no statistical conclusions could be tested from this study.

4. Study 8297 – An open-label, randomized, dose-finding, cross-over multi-center trial in Spain that included thirty-eight patients with serum LH of less than 1.2 IU/L were entered into the trial and could receive up to three cycles of therapy. Patients were recruited into a single-arm from seven sites were randomized to a treatment sequence, that began with 75 IU. Treatment was with 75, 150 and 225 IU doses of Luveris® in a sequential order. However, only the first cycle of treatment is considered primary for efficacy.

Analysis of success of follicular development (8297)	Luveris® 75 IU	p-value
Sponsor's (Evaluable) %	82%	N/A**
Division's re-analysis (ITT)* %	55%	N/A**

*As opposed to the Sponsor, the Division excluded all subjects from analysis that had a risk of ovarian hyperstimulation. These subjects who did not complete treatment cycles were considered failures.

**This is a small exploratory study, and no statistical conclusions could be tested from this study.

CLINICAL REVIEW

Clinical Review Section

Appendix

C. Overview of Completed Clinical Trials for NDA 21-322 (Continued):

5. Study 21008 – A randomized, double-blind, placebo-controlled, parallel-arm, multi-center trial conducted world-wide that included thirty-nine patients with serum LH of less than 1.2 IU/L were entered into the trial and could on cycle of therapy. Patients were recruited from twenty-five sites and were randomized 2:1 basis to Luveris® (75 IU) or a placebo.

Analysis of success of follicular development (7798)	Placebo	Luveris® 75 IU	p-value
Sponsor's (Evaluable) %	20%	67%	0.023 (Fisher's)
Division's re-analysis (ITT)* %	8%	38%	0.063 (Fisher's)

*As opposed to the Sponsor, the Division excluded all subjects from analysis that had a risk of ovarian hyperstimulation. These subjects who did not complete treatment cycles were considered failures.

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On Original

CLINICAL REVIEW

Clinical Review Section

Appendix

D. References for this review:

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CLINICAL REVIEW

Clinical Review Section

Appendix

D. References (continued):

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CLINICAL REVIEW

Clinical Review Section

Appendix

E. Phase 4 Protocol Outline

Title: “A phase 4 clinical trial to confirm the efficacy of the 75 IU dose of Luveris® versus placebo when co-administered with follitropin alfa for induction of follicular development and pregnancy in hypogonadotropic hypogonadal women with profound LH deficiency, as defined by a baseline LH level < 1.2 IU/L.”

Primary Objective:

- To confirm the efficacy of the 75 IU dose of Luveris® compared to Placebo administered concomitantly with follitropin alfa for induction of clinical pregnancy in women with hypogonadotropic hypogonadism and profound LH deficiency (< 1.2 IU/L).

Study Summary:

Briefly, this is a placebo-controlled, randomized, two-arm parallel study that will enroll 120 women with hypogonadotropic hypogonadism (60 per group). Inclusion criteria include subjects with a history of WHO Group I type anovulation with a serum FSH < 5 IU/L and a serum LH < 1.2 IU/L. Subjects who appear to be eligible will be randomized in a 1:1 ratio to receive Luveris® 75 IU or a Placebo and concomitant follitropin alfa (Gonal-f®). Patients will be treated for up to three ovulation induction cycles, with a maximum of one rest cycle between each cycle.

The primary objective of this study is to determine the efficacy of 75 IU of Luveris® compared to a placebo by comparing the clinical pregnancy rate. The primary efficacy endpoint is the cumulative per patient clinical pregnancy rate over three treatment cycles. The duration of the study will be approximately 3 treatment cycles, each having a maximum treatment duration totaling up to 21 days, with a rest period in between each cycle of no more than 42 days.

Safety will be assessed by serum laboratory evaluations and monitoring for adverse events. An outline of the study design is attached as Appendix - F. New Phase 4 Study Protocol - Figure 1.

Overview of the Study Design:

The Sponsor has proposed a three cycles, multi-center, phase III clinical study that will enroll at least 120 subjects (60 per treatment group) that will complete three cycles of gonadotropin treatment. The study will recruit subjects with a history of profound hypogonadotropic hypogonadism (as defined by a serum LH < 1.2 IU/L). These subjects will be screened for the inclusion criteria and undergo a pre-screening evaluation to make sure that she meets the study's eligibility criteria and to obtain baseline laboratory measurements. Subjects who meet the inclusion criteria be randomized in a 1:1 manner to receive 75 IU of Luveris® or Placebo.

CLINICAL REVIEW

Clinical Review Section

Study Design (continued):

In addition, to Luveris® or Placebo, follitropin alfa will be given at a fixed dose of 150 IU for the first 7 days of treatment cycle 1. From Day 8 of treatment onward, the follitropin alfa dose can be adjusted in multiples of 37.5 IU according to the ovarian response. Follitropin alfa and Luveris® will be co-administered as one injection, both by the subcutaneous route.

The total length of gonadotropin treatment cannot exceed 14 days unless serum estradiol levels and/or follicular growth indicate imminent follicular development (follicle size ≥ 14 mm). Patients can be treated for a maximum of 21 days per cycle. When follicular response is adequate, ovulation will be triggered by a subcutaneous injection of Ovidrel® (250 mcg of choriongonadotropin alfa). Luteal phase function and ovulation will be assessed by serum progesterone measurements, following which luteal support using Crinone® (a vaginally administered progesterone) will be given after the serum progesterone measurement is obtained. Luteal phase progesterone support will be administered with one dose of Crinone® administered daily vaginally. Luteal phase support with Crinone® will continue until menstruation or for at least 30 days after the pregnancy is confirmed by laboratory evidence. In treatment cycles 2 and 3, the starting dose of follitropin alfa for the first 7 days can be adjusted (upwards or downwards) based on the response in previous cycle(s). From day 8 onward, the follitropin alfa dose may be adjusted in multiples of 37.5 IU according to the ovarian response. In all cycles of treatment, Luveris® will remain constant at 75 IU.

Safety will be assessed in each treatment cycle by monitoring laboratory and adverse events. All subjects will have a post-study visit on the 2-4 weeks following administration of Ovidrel® that will include a general physical examination and collection of routine safety laboratories including hematology, clinical chemistry and urinalysis. A detailed overview of the study visits and procedures is attached as Appendix – F. New Phase 4 Protocol Study - Figure 1.

Reviewer's comment: This reviewer recommends that the Sponsor record the diagnosis of each patient entering the trial, rather than just listing primary or secondary amenorrhea as had been done in previous studies of Luveris®. I also recommend that the Investigators record the results of the baseline semen analysis (number of total sperm and percentage motile sperm).

Key Inclusion Criteria:

- Clinical history of hypogonadotropic hypogonadism (WHO Group I) on the basis on congenital or acquired hypothalamic or pituitary or endocrine dysfunction in the presence of qualifying screening laboratories.
- Have no prior treatment cycles with gonadotropins or gonadotropin-releasing hormone (GnRH) – gonadotropin naïve
- Have primary or secondary amenorrhea
- Negative progesterone challenge test
- When indicated, have a normal computer tomography (CT) scan or nuclear magnetic resonance (NMR) scan of the hypothalamic-pituitary region on file
- Have a body mass index between 18.4 and 31.4 kg/m²

CLINICAL REVIEW

Clinical Review Section

Key Inclusion Criteria (continued):

- The following hormonal values in a centrally analyzed fasting blood sample drawn within 6 weeks before initiation of treatment:
 - Serum follicle stimulating hormone (FSH): < 5 IU/L
 - Serum luteinizing hormone (LH): < 1.2 IU/l
 - Serum estradiol (E2): < 60 pg/mL (< 220 pg/L)
 - Serum prolactin (PRL): < 43.3 ng/mL (<1040 mIU/L)
 - Serum thyroid stimulating hormone (TSH): < 6.5 mIU/mL
 - Free T4: 0.8 – 1.8 ng/dL (11-24 pmol/L)
 - Testosterone: < 1.0 ng/mL (<3.5 nmol/L)

Reviewer's comments:

1. *This reviewer recommends increasing the age for inclusion criteria to 40 years of age.*
2. *This reviewer recommends that patients undergoing in vitro fertilization, intracytoplasmic injection or any other concomitant experimental treatment be excluded from the study.*
3. *This reviewer recommends that the inclusion criteria for estradiol be lowered to a serum estradiol level less than 20 pg/mL.*

Key Exclusion Criteria:

- Known active substance or eating disorder
- Central nervous system (CNS) lesions: In cases where hypogonadotropic hypogonadism is secondary to a CNS lesion or its treatment, the patient will not be eligible without consulting Serono's medical director
- Exercise program exceeding 10 hours/week
- Currently undergoing treatment with psychotropic medication or any medication known to interfere with normal reproduction (e.g. neuroleptics, dopamine antagonists).

Efficacy Endpoints:

The primary endpoint is the cumulative clinical pregnancy rate (defined as fetal sac with heartbeat on ultrasound in up to three treatment cycles).

Secondary endpoints include:

- Follicular development as assessed by:
 - At least one follicle ≥ 17 mm in diameter on ultrasound
 - Preovulatory serum estradiol level of ≥ 109 pg/mL
 - Mid-luteal phase progesterone of ≥ 7.9 ng/mL
- Ovulation as defined as a mid-luteal progesterone ≥ 10 ng/mL with the higher of two progesterone values used in the efficacy analysis. Ovulation is assumed to have occurred in any patient that has a positive pregnancy test (Serum β -hCG of ≥ 10 mIU/mL)
- Overall pregnancy rate as determined by serum pregnancy test on cycle day 15-20; if the serum β -hCG is ≥ 10 mIU/mL, the test will be repeated 3-4 days later to confirm pregnancy

CLINICAL REVIEW

Clinical Review Section

Reviewer's comments:

1. *This reviewer would also include in the secondary efficacy endpoints:*
 - *Mean estradiol values on the day of hCG*
 - *Cycle cancellation rate*
 - *Livebirth rate*
 - *Total vials of gonadotropin use per cycle*
 - *Total duration of gonadotropin use*
 - *Rate of spontaneous abortion*
 - *Rate of ectopic pregnancy*
2. *This reviewer does not agree with the Sponsor's definition of overall pregnancy rate. The Sponsor has presented a definition of a biochemical pregnancy rate. This reviewer recommends that the Sponsor determine overall pregnancy rate as the proportion of patients who demonstrate a doubling of serum β -hCG over 48 to 72 hours.*
3. *This reviewer (as discussed previously) does not concur with the Sponsor's criteria for follicular development.*
4. *The reviewer notes that the Sponsor has listed a standard method of measuring endometrial thickness. Although this is clearly a research tool, it may be important to evaluate as an endpoint.*

Consent Form:

An informed consent form was not submitted.

Safety Considerations and Endpoints:

Safety will be assessed primarily by monitoring for adverse events at each study visit. The study dates for measurement of complete blood count, serum chemistries, serum liver function and physical examination are in the protocol at baseline and post-treatment (2-4 weeks following human chorionic gonadotropin (hCG) injection; if hCG not given, within 2 weeks of the last dose of FSH/LH or FSH/placebo (See Appendix – F. Overview of Phase 4 Protocol [Figure 1]). Periodic examinations and adverse experiences will be monitored during the treatment phase and post-treatment (See Appendix – F. Figure 1).

Reviewer's comments:

1. *This reviewer concurs that the Sponsor has adequately standardized the grading of ovarian hyperstimulation syndrome. However, I recommend that the Sponsor classify as severe any patient that was hospitalized for OHSS or required aggressive therapeutic intervention (including albumin and paracentesis). This classification concurs with a recent American Society of Reproductive Medicine publication of the findings in patients with severe ovarian hyperstimulation syndrome.²⁰*
2. *I recommend that the safety endpoints should also include:*
 - *Incidence of multi-fetal gestation*
 - *Incidence of fetal anomalies*
 - *Incidence of second and third trimester fetal loss*
 - *Incidence of birth defects*

CLINICAL REVIEW

Clinical Review Section

Termination criteria include:

- Serious adverse event that is drug related
- Pregnancy
- Moderate to severe ovarian hyperstimulation syndrome (OHSS)
- Major protocol violations – including non-compliance and lost to follow-up
- Serious intercurrent illness or significant worsening of intercurrent illness
- Patient choice (withdrawn consent)
- Administrative reasons

Reviewer's comments: The Sponsor has stated that a patient will discontinue Luveris®/Placebo/FSH and/or Ovidrel® treatment for any of the following reasons:

- *Treatment Failure: Defined as no ovarian response after 14 days of treatment, unless follicular size (≥ 14 mm) indicates imminent follicular development.*
- *Risk of ovarian hyperstimulation syndrome (OHSS): Defined as an ultrasound scan showing more than 3 follicles, each with a diameter of ≥ 15 mm and a serum estradiol level of greater than or equal to 2000 pg/mL. In such a case, human chorionic gonadotropin must be withheld.*

This reviewer has concerns that:

- 1. The Sponsor continues to count patients cancelled for an adverse event (OHSS) as a success. This reviewer disagrees that an adverse event should be treated as a success.*
- 2. The Sponsor has stated that one of the discontinuation criteria includes a serum estradiol level of greater than or equal to 2000 pg/mL. The current recommendations from the American Society of Reproductive Medicine suggest that the cut-off level could be raised to 2,500 pg/mL.²⁰ The reviewer has concerns that although the Sponsor may decrease the number of patients with the adverse event of ovarian hyperstimulation, the Sponsor will increase the cycle cancellation rate. However, as a sole predictor of OHSS, serum estradiol is poor (approximately 85% in one published study).²¹ Therefore, although the Sponsor is conservative with the estradiol cut-off level, in this reviewer's opinion, the cut-off is acceptable provided that the cycle cancellation rate does not exceed 14% of total cycles as is seen in the 2001 National US Statistics for ART.²²*

Statistical considerations:

Primary outcome variable is the cumulative per patient clinical pregnancy rate over three cycles.

Secondary outcome variables include:

- Follicular development
- Ovulation
- Pregnancy rate

CLINICAL REVIEW

Clinical Review Section

Statistical considerations (continued):

Reviewer's comments:

1. *The Sponsor refers to an overall pregnancy rate using a serum β -hCG of ≥ 10 mIU/mL. This reviewer considers a positive serum pregnancy test as a biochemical pregnancy rate, and would consider it a positive if there was a doubling of serum β -hCG over 48-72 hours.*
2. *This reviewer would add the following secondary efficacy variables: Mean estradiol values on the day of hCG, Cycle cancellation rate, Livebirth rate, Total vials of gonadotropin use per cycle, Total duration of gonadotropin use, Rate of spontaneous abortion and Rate of ectopic pregnancy.*

Sample Size: The Sponsor anticipates a dropout rate of 31%. The Sponsor has calculated that 120 patients will need to be enrolled to allow a sample size of 82 total patients to complete the study (41 per treatment arm).

The Sponsor has defined the ITT population as patients who have received at least one injection of randomized treatment. The efficacy outcomes will be analyzed separately for each treatment group. All statistical tests will be 2-sided and performed at the 5% significance level. Cumulative clinical pregnancy rate over three cycles of treatment, the primary efficacy endpoint, will be compared using the 75 IU of Luveris® and Placebo treatment groups using Fisher's Exact Test. Patients who are not pregnant and who drop out of the study prior to completing three cycles will be counted as failures. Secondary endpoints including follicular development and ovulation in the first cycle, as well as cumulative follicular development and ovulation rates over three cycles will be compared using the 75 IU Luveris® and Placebo treatment groups using Fisher's Exact Test. Follicular development will be analyzed counting cycle cancellations and the risk of OHSS both as a failure and a success.

Reviewer's comments:

1. *We recommend that the primary efficacy analysis be an intent-to-treat analysis of time from randomization to the occurrence of a clinical pregnancy, recognized as a gestational sac with fetal heart motion on vaginal ultrasound at 6 weeks post-embryo transfer. We recommend a two-sided 95% or one-sided 97.5% confidence interval analysis of the difference. To demonstrate efficacy, we recommend that the lower bound of the confidence interval be equal to or no greater than one month.*
2. *This reviewer would propose that patients that use more than 75 IU of Luveris® be excluded from this analysis.*

Reviewer's Comments Regarding the Phase 4 Protocol:

- The study is reasonably safe to proceed.
- The study objectives are clear and based on sound rationale.
- The study protocol appears adequate to provide some data towards achieving the objectives of the study.
- The risks of the study are adequately appreciated.
- Adequate precautions are being maintained.

CLINICAL REVIEW

Clinical Review Section

Clinical Remarks:

We have the following comments regarding the proposed Phase 4 study, titled “A phase 4 clinical trial to confirm the efficacy of the 75 IU dose of Luveris® versus placebo when co-administered with follitropin alfa for induction of follicular development and pregnancy in hypogonadotropic hypogonadal women with profound LH deficiency, as defined by a baseline LH level < 1.2 IU/L.”:

1. We recommend that this study be designed to look for the lowest effective dose and that it evaluate a dose of Luveris® lower than 75 IU in addition to the 75 IU dose.
2. We recommend that the primary efficacy analysis be an intent-to-treat analysis of time from randomization to the occurrence of a clinical pregnancy, recognized as a gestational sac with fetal heart motion on vaginal ultrasound at 6 weeks post-embryo transfer. We recommend a two-sided 95% or one-sided 97.5% confidence interval analysis of the difference. To demonstrate efficacy, we recommend that the lower bound of the confidence interval be equal to or no greater than one month. We continue to recommend that patients who are cancelled for the risk of ovarian hyperstimulation syndrome be considered treatment failures.
3. We recommend that per cycle clinical pregnancy rate analyses and cumulative cycle analyses be considered secondary analyses.
4. We recommend that the specific clinical diagnosis of each patient entering the trial be recorded in detail, rather than categorizing as primary or secondary amenorrhea.
5. We recommend that you record in detail the results of the baseline semen analysis (number of total sperm and percentage motile sperm).
6. We recommend increasing the age for inclusion criteria to 40 years of age.
7. We recommend excluding patients undergoing in vitro fertilization, intracytoplasmic injection or any other concomitant Assisted Reproductive Technology procedure other than intrauterine insemination.
8. We recommend that the inclusion criteria for estradiol be lowered to a serum estradiol level < 20 pg/mL.
9. We do not agree with your definition of overall pregnancy rate. You have presented the definition of a biochemical pregnancy rate. We recommend defining overall pregnancy rate as the proportion of patients who demonstrate a doubling of serum β -hCG over 48-72 hours.
10. We propose patients that have had their Luveris® dose titrated be excluded from this analysis.
11. We recommend a classification of severe ovarian hyperstimulation syndrome (OHSS) for any patient that is hospitalized or requires aggressive treatment (such as albumin or paracentesis).

CLINICAL REVIEW

Clinical Review Section

Clinical Remarks (continued):

12. We recommend inclusion of the following secondary efficacy endpoints:
 - Mean estradiol values on the day of hCG
 - Cycle cancellation rate
 - Livebirth rate
 - Total vials of gonadotropin use per cycle
 - Total duration of gonadotropin use
 - Rate of spontaneous abortion
 - Rate of ectopic pregnancy
13. We do not concur with your hormonal criteria for follicular development, and you have not provided adequate literature support for your choice of cut-off values. The Division recommends more stringently defined (as supported by the literature) minimal (cut-off) levels for serum estradiol and progesterone levels (serum estradiol levels of ≥ 200 pg/mL and serum progesterone levels ≥ 10 ng/mL) to achieve successful follicular development.
14. We recognize that measuring endometrial thickness is a research tool; however, we recommend that endometrial thickness be assessed as a secondary efficacy endpoint.
15. We recommend that additional safety endpoints should also include:
 - Incidence of multi-fetal gestation
 - Incidence of fetal anomalies
 - Incidence of second and third trimester fetal loss
 - Incidence of birth defects

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CLINICAL REVIEW

Clinical Review Section

Appendix

F. Overview of Phase 4 Protocol - Figure 1

Pre-study evaluation (Within 6 weeks of the start of study treatment)	Treatment Cycle Assessment	S1	S5	S7	Sn*	DhCG	DhCG4-5 and DhCG 6-7	DhCG 15-20 and DhCG 18-24	DhCG 35-42	Post-Study Assessments (2-4 weeks following hCG; if hCG not given, within 2 weeks of study treatment)
Demographics	B-hCG	X						X		Physical Exam Central labs (Safety)
Medical history	E2- local lab	X	X	X	X	X				
Ob/Gyn history	E2 – central lab	X	X	X	X	X				
Physical Exam	Ultra- sound	X	X	X	X	X				
Gyn Exam	P4 – central lab						X			
Ultrasound	Adverse event monitoring	X	X	X	X	X	X	X		
Central hormone and safety laboratories	Monitoring of concomitant meds/ procedures	X	X	X	X	X	X	X		
Progesterin challenge test										
Semen analysis										
Pituitary CT/ MRI scan (if indicated)										
Randomization ¹										

Sn* - After S7, patients should be monitored every 2-3 days until the lead follicle reaches 14 mm. Thereafter, patients should be monitored every 1-2 days until day of hCG.

1 - randomization will take place no earlier than 3 days prior to S1

E2 - estradiol, P4 - progesterone, hCG - human chorionic gonadotropin, CT- Cat Scan, MRI - Magnetic Resonance Imaging Scan, Gyn - gynecologic

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/s/

Audrey Gassman
9/28/04 02:20:26 PM
MEDICAL OFFICER

Shelley Slaughter
10/6/04 01:42:30 PM
MEDICAL OFFICER
I concur.

NDA: 21-322
Drug: Luveris® (lutropin alfa for injection)
Sponsor: Serono, Inc.

Safety Update Review

Refer to the Medical Officer's review.

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Luveris™
Team Leader Memorandum
Addendum - Post Advisory Committee
Study 21445

NDA: 21-322

Drug: Luveris™ (recombinant human Luteinizing Hormone [r-hLH])

Indication: Concomitant administration along with recombinant human follicle stimulating hormone (r-hFSH) for the induction of ovulation in infertile women with severe LH (< 1.2) ζ deficiency.

Dosage/Form/Route: 75 IU sterile lyophilized powder to be reconstituted with 1 ml Sterile Water for Injection. A single 75 IU dose is administered via subcutaneous injection once daily until estradiol and ultrasound monitoring indicate ζ hCG should be given to complete follicular development and effect ovulation. FSH should be administered concomitantly with Luveris™

Applicant: Serono Laboratories, Inc

Original Submission Date: May 1, 2001

N-000BZ for Study 21445: April 29, 2003

Primary Review Completed: September 4, 2003

Concurrence: September 4, 2003

Date of Memorandum: April 22, 2004

Background and Regulatory History:

On March 1, 2002, the Division of Reproductive and Urologic Drug Products made a Not Approvable decision for NDA 21-322 for Luveris™ for the indication of induction of ovulation in hypogonadotropic hypogonadal infertile women with severe LH (< 1.2) ζ deficiency. The reader is referred to the primary Medical Officer and the Team Leader reviews, dated March 01, 2002, for details on the findings of efficacy and safety. A post-decision meeting was held with Serono on May 10, 2002. At that meeting the Division proposed that the Sponsor conduct a new Phase 3 study that would address ovulation rates for subjects receiving the 75 IU dose and one or more lower doses. Instead the Sponsor proposed to submit the data from Study 21415, an extension study to Study 21008. The Division relayed to the Sponsor that post-hoc analyses on Study 21415 was insufficient to address the Division's concerns regarding efficacy that led to the Not Approvable decision. In addition, the open labeled, uncontrolled design of Study 21415 made it unacceptable as a "pivotal" study. The Division conveyed to the Sponsor that they had the options of either appealing the Division's decision to the Office of Drug Evaluation 3 or they could submit for review a protocol for a new study.

On January 9, 2003, a second post-decision discussion via teleconference was held with the Sponsor. The Division reiterated its position from the May 10, 2002 meeting that efficacy had not been established and the Sponsor could appeal the decision or conduct a new study. The Sponsor was also given the additional option of discussing their application at an upcoming meeting of the Advisory Committee for Reproductive Health. The Sponsor opted to have the application discussed before the Advisory Committee. Luveris™ was discussed on September 30, 2003, the second day of a two-day meeting of the Reproductive Health Committee. After hearing presentations from experts in Reproductive Endocrinology on the subject of female hypogonadotropic hypogonadism as well as the presentations from the Division and the Sponsor on the efficacy data for Luveris™, the Committee was asked to discuss the application and vote. The Committee voted 15 to 0 that the Sponsor's data did not demonstrate efficacy for Luveris™ in ovulation induction when the primary endpoint was ovulation rate. The Committee voted 8 to 7 that the Sponsor's data demonstrated efficacy for Luveris™ in ovulation induction when the primary endpoint was follicular development. Finally, the Committee voted 11 to 3 (one committee member had left the proceedings) that the Sponsor's data demonstrated efficacy for Luveris™ for follicular development when the primary endpoint was follicular development.

Following the Advisory Committee Meeting, the Division committed to taking a closer look at Study 21415 in its process of addressing Serono's request for reconsideration of the Division's Not Approvable decision for NDA 21-322.

Study 21008 (multinational)

Study 21415 was a prospective, **non-randomized, open-label**, multi-center study conducted in 25 centers throughout the U.S., Canada, Israel and Australia. Subjects who had previously been treated in Study 21008 but had not achieved a clinical pregnancy were recruited. The study objectives were to collect additional pregnancy data for subjects receiving the 75 IU dose of Luveris™ concomitantly with r-hFSH.

Multiple (up to three) cycles of treatment were evaluated. Like Study 21008, the Sponsor evaluated as a primary efficacy endpoint the achievement of adequate follicular development as defined by the following three criteria, all of which should be satisfied.

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

Prior to the conduct of the Phase 3 study, Study 21008, the Division offered strong recommendations to the Sponsor on multiple occasions that only the ovulation rate (as determined by the percentage of subjects achieving a mid-luteal progesterone level ≥ 10 ng/ml) be used as the primary endpoint. The Sponsor chose not to follow these recommendations in their selection of the combined endpoint of follicular development (and the definition of the individual components of the combined endpoint).

During the extension study, Study 21415, unlike the Phase 3 study, Study 21008, the investigators were allowed to titrate the FSH to response (i.e. not a fixed dose of FSH as in Study 21008). Patients received their dose administered as either two separate injections of r-hFSH and r-hLH or as one injection of r-hFSH and r-hLH combined. The study enrolled a total of 31 eligible premenopausal, hypogonadotropic (serum FSH < 5 , serum LH < 1.2 and serum $E_2 < 60$ pg/ml) hypogonadal women, aged 18 to 39, who desired pregnancy.

Table 1 presents the amenorrhea classification (primary vs. secondary) and diagnosis for subjects entered into Study 21415 compared to the Phase 3 study, Study 21008.

Table 1 – Primary Infertility Diagnosis Breakdown of Studies 21415 and 21008

Primary diagnosis	Study 21415	Study 21008
N (completed study)	N=31	N=39
Hypothyroidism	3 (10%)	3 (7%)
Hypothalamic Amenorrhea	2 (6%)	2 (5%)
Kallmann's	4 (13%)	3 (7.7%) (1 withdrew)
Panhypopituitarism	1 (3%)	1 (3%)

Tables 2 through 4 display the follicular development and clinical pregnancy rates seen in Study 21415. Tables 3 and 4 present the same data from Study 21008 for comparison.

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Table 2 -- Intent-to Treat Subjects from Study 21415

	Study 21415 75 IU r-hLH (1 st cycle n=31)
Primary Efficacy Variable: Protocol Definition: OHSS=success Follicular Development Success (%) Failure (%)	 21 (67.7%) 10 (32.3%)
Primary Efficacy Variable: Reclassify OHSS=failure Follicular Development Success (%) Failure (%)	 16 (51.6%) 15 (48.4%)
Secondary Efficacy Variables:	
Follicle Size: At Least One Follicle \geq 17 mm Success (%) Failure (%)	 26 (83.9%) 5 (16.1%)
Pre-Ovulatory E ₂ Level \geq 109 pg/mL Success (%) Failure (%)	 26 (83.9%) 5 (16.1%)
Mid-Luteal P ₄ Level \geq 7.9 ng/mL Success (%) Failure (%)	 18 (58.1%) 13 (41.9%)
Clinical Pregnancy Success (%) Failure (%)	 11(35.5%) 20(64.5%)
Risk of OHSS Yes (%) No (%)	 5(16.1%) 26(83.9%)
Endometrial thickness (mm) Mean (S.D.)	 9.6(1.4)

Table 3 – Intent-to Treat Subjects Comparing Results Studies 21415 and 21008

	Study 21415 75 IU r-hLH (1 st cycle n=31)	Study 21008 Placebo (n=13)	Study 21008 75 IU r-hLH (n=26)
Primary Efficacy Variable: Protocol Definition: OHSS=success Follicular Development Success (%) Failure (%)	21 (67.7%) 10 (32.3%)	2 (15%) 11 (85%)	16 (62%) 10 (38%)
Primary Efficacy Variable: Reclassify OHSS=failure Follicular Development Success (%) Failure (%)	16 (51.6%) 15 (48.4%)	1 (8%) 12 (92%)	10 (38%) 16 (62%)
Secondary Efficacy Variables:			
Follicle Size: At Least One Follicle \geq 17 mm Success (%) Failure (%)	26 (83.9%) 5 (16.1%)	4 (31%) 9 (69%)	16 (62%) 10 (38%)
Pre-Ovulatory E ₂ Level \geq 109 pg/mL Success (%) Failure (%)	26 (83.9%) 5 (16.1%)	2 (15%) 11 (85%)	16 (62%) 10 (38%)
Mid-Luteal P ₄ Level \geq 7.9 ng/mL Success (%) Failure (%)	18 (58.1%) 13 (41.9%)	2 (15%) 11 (85%)	12 (46%) 14 (54%)
Clinical Pregnancy Success (%) Failure (%)	11(35.5%) 20(64.5%)	1 (8%) 12 (92%)	1 (4%) 25 (96%)
Risk of OHSS Yes (%) No (%)	5(16.1%) 26(83.9%)	1 (8%) 12 (92%)	6 (23%) 20 (77%)
Endometrial thickness (mm) Mean (S.D.)	9.6(1.4)	4.1(2.9)	6.7(3.2)

Table 4: Intent-to Treat Subjects in 1st treatment cycle of 21415 (only Luveris™ naïve patients) compared to Study #21008

	Study 21415 naïve patients (n=11)	Placebo (n=13)	75 IU r-hLH (n=26)
Primary Efficacy Variable: Protocol Definition: OHSS=success			
Follicular Development			
Success (%)	7(64%)	2 (15%)	16 (62%)
Failure (%)	4(36%)	11 (85%)	10 (38%)
p-value vs. placebo (Fisher's Exact Test)			
Primary Efficacy Variable: Reclassify OHSS=failure			
Follicular Development			
Success (%)	5(45%)	1 (8%)	10 (38%)
Failure (%)	6(55%)	12 (92%)	16 (62%)
p-value vs. placebo (Fisher's Exact Test)			
Secondary Efficacy Variables:			
Follicle Size:			
At Least One Follicle ≥ 17 mm			
Success (%)	8(73%)	4 (31%)	16 (62%)
Failure (%)	3(27%)	9 (69%)	10 (38%)
p-value vs. placebo (Fisher's Exact Test)			
Pre-Ovulatory E ₂ Level ≥ 109 pg/mL			
Success (%)	8(73%)	2 (15%)	16 (62%)
Failure (%)	3(27%)	11 (85%)	10 (38%)
p-value vs. placebo (Fisher's Exact Test)			
Mid-Luteal P ₄ Level ≥ 7.9 ng/mL			
Success (%)	6(55%)	2 (15%)	12 (46%)
Failure (%)	5(45%)	11 (85%)	14 (54%)
p-value vs. placebo (Fisher's Exact Test)			
Clinical Pregnancy			
N (patients who desired pregnancy)	11		
Success (%)	4 (36%)	1 (8%)	1 (4%)
Failure (%)	7 (64%)	12 (92%)	25 (96%)
p-value vs. placebo (Fisher's Exact Test)			
Risk of OHSS			
Yes (%)	1 (9%)	1 (8%)	6 (23%)
No (%)	10 (91%)	12 (92%)	20 (77%)
p-value vs. placebo (Fisher's Exact Test)			

Source: SAS datasets

When Luveris™-naïve subjects whose cycles were cancelled for the risk of OHSS are **not** counted as successes for follicular development, the follicular development rate in Study 21415 is 45% compared to a 38% rate in Luveris™ subjects in Study 21008 and 8% in placebo subjects from Study 21008. The clinical pregnancy rate in the first cycle was 36% (4 subjects), 4% (1 subject) and 8% (1 subject), respectively. Over three cycles of treatment, the clinical pregnancy

rates for Luveris™-treated subjects in Study 21415 were 35.5% (11 subjects) in the first cycle, 33.3% in cycle 2 (5 subjects) and 0% in cycle 3. Study 21415 had no control r-hFSH-only subjects to determine the respective rates of follicular development and clinical pregnancy rates, when investigators were allowed to titrate FSH to response in these subjects.

Tables 5 through 7 present pregnancy information on the subjects who conceived in Study 21415. Tables 5 and 6 presents the category (primary vs. secondary) of amenorrhea for those subjects who conceived in Study 21415. Table 6 also presents the specific diagnosis reported by the Sponsor for those subjects. Table 7 presents the information for those subjects who might be expected to have the most severe deficit of gonadotropins.

Table 5 – Amenorrhea Status for Women Achieving Clinical Pregnancy in Study 21415

Amenorrhea	Cycle 1	Cycle 2	Total
Primary	6 clinical pregnancies (6 of 16 patients)	2 clinical pregnancies	8 clinical pregnancies in primary group
Secondary	5 clinical pregnancies (5 of 15 patients)	3 clinical pregnancies	8 clinical pregnancies in secondary group
Total	11 pregnancies	5 clinical pregnancies	16 total clinical pregnancies in 54 total cycles (29.6% per cycle)

Table 6 - Diagnosis and Amenorrhea Status for Women Achieving Clinical Pregnancy in Study 21415 Reported per Enrollment Number

Patient Number	Amenorrhea	Diagnosis	Gravida	Parity	Preg in Cycle Number (#)
2520001	Primary	Anosmia	0	0	1
2640001	Primary	*	0	0	1
0480001	Primary	Primary Amenorrhea	0	0	1
1090001	Primary	Anosmia	0	0	1
2580003	Primary	*	0	0	1
4380002	Primary	*	0	0	1
2830001	Primary	Infertility	0	0	2
3920003	Primary	*	0	0	2
2620002	Secondary	Hypothyroidism	2	0	1
4180002	Secondary	Pituitary resection	2	2	1
4170001	Secondary	*	0	0	1
4360001	Secondary	*	0	0	1
4390001	Secondary	Amenorrhea	1	0	1
3920005	Secondary	*	1	1	2
2520002	Secondary	*	0	0	2
4180003	Secondary	*	0	0	2

*No diagnosis in dataset

Table 7—Pregnancies by Primary Diagnosis for selected patients with amenorrhea and an additional diagnosis of interest for Study 21008

	Study 21008	Study 21415
Patient Number (Diagnosis)	Pregnancy/Group	Pregnancy/Group
1270001 (Kallmann's)	N (LH group)	N
1270002 (Kallmann's)	N (LH group)	N
1280005 (Kallmann's)	Withdrawn/allergic reaction	N
2620001 (Kallmann's)	N (LH)	N
2510001 (Anosmia)*	N (LH)	N
2520001 (Anosmia)	N (Placebo)	Y
1090001 (Anosmia)*	N (LH)	Y
2530003 (Hypothalamic Amenorrhea)	N (LH)	N
2620003 (Hypothalamic Amenorrhea)	N (Placebo- 2 amenorrhea**)	N
4340002 (Panhypopituitarism)	N (Placebo)	N

*It is unclear whether these patients had Kallmann's or another disorder.

** This patient also had hirsutism and it is unclear what the underlying disorder was

One notes that of the 16 total subjects who conceived, 8 of these have a diagnosis of secondary amenorrhea. Four (4) of these secondary amenorrhea subjects were previously pregnant. Of the primary amenorrhea subjects, none were specifically reported as having Kallmann's syndrome (the primary amenorrhea diagnosis where there is no GnRH and thus the absence of gonadotropins). Therefore, it is impossible to know how these women with no gonadotropins would have fared in this study.

The Sponsor in its briefing document to the Advisory Committee reported a 51.6% cumulative clinical pregnancy rate after 3 cycles of treatment. This is not a true per cycle analysis and not all cycles were accounted for in this rate. The American Society for Reproductive Medicine, the professional society representing specialists in reproductive endocrinology and infertility, recommends that the reporting of statistics for ART procedures must include all initiated cycles and their outcomes. They further stipulate that the method used to calculate success rates must report both a numerator and a denominator. Looking at the clinical pregnancy rate from Study 21415 in this way, there were 16 total pregnancies in 54 cycles yielding a rate of 29.6%/cycle initiated.

Discussion and Conclusions

The data collected in Study 21415 does not provide sufficient additional evidence to support efficacy for Luveris™ in ovulation induction and pregnancy. The study suffers from a number of inherent flaws. It was a non-controlled, non-randomized study. Unlike Study 21008, investigators were allowed to titrate the dose of r-hFSH, yet no r-hFSH alone arm was included to compare how these subjects would have done compared to those receiving Luveris™ plus r-hFSH. In Study 21415, there was a 35 % clinical pregnancy rate (Luveris™-treated subjects) after the first cycle and an overall 29.6%/cycle clinical pregnancy rate in the study, but again lack of a control arm blurs the interpretation of that rate. One must wonder whether pregnancies are occurring as a result of Luveris™ treatment or do the pregnancies result from FSH treatment when the dose of FSH can be titrated to effect as was done in this study. Arguing in favor that the

latter is a possibility, 3 out of 9 women with hypogonadotropic hypogonadism ($LH \leq 1.2$) ovulated when treated with FSH-alone (dosage titrated and not fixed) in a small cross over study of human menopausal gonadotropin (HMG) vs. FSH (Shoham et al. 1991 Fertility and Sterility vol. 56, p 1048).

In Study 21415, there were no pregnancies in individuals diagnosed with Kallmann's syndrome. Kallmann's is a form of isolated hypogonadotropic hypogonadism in which anosmia or hyposmia from agenesis of the olfactory lobe is associated with GnRH deficiency. It was surprising that none of the women with this diagnosis were found to have conceived in Study 21415 because these are the individuals that would be expected to respond well to exogenous LH if indeed it is required. A recent case report by Battaglia et al. (2000 Fertility and Sterility vol. 73 , p. 284) described a successful ovulation induction and clinical pregnancy in a woman with Kallmann's syndrome ($LH 1.1$ IU/l and $FSH 1.7$ IU/L) treated with highly purified FSH alone when the dose of FSH was allowed to be titrated. While one must be careful not to over-interpret the results from a single case report, I think this an important case report in that it demonstrates that even a Kallmann's patient with absent GnRH might respond to FSH-alone when the dose of FSH is titrated.

I continue to believe that the Sponsor has not provided a body of data to unequivocally support efficacy for Luveris™ ($LH < 1.2$) in treatment of hypogonadotropic hypogonadal women with severe LH deficiency. While, I continue to believe that LH may be required for the induction of ovulation and pregnancy in some sub-population of hypogonadotropic hypogonadal women, I have some concern that we can not yet detect that population with the current markers available. I concur with the clinical reviewer and I continue to recommend that this NDA not be approved.

The clinical review team made a previous recommendation that a new Phase 3 clinical trial be conducted to address the deficiency in efficacy data. We continue to support this recommendation. This study must be appropriately powered to demonstrate whether Luveris™ doses are statistically different from placebo (FSH-alone) for ovulation induction in hypogonadotropic hypogonadal women with profound LH deficiency. I believe that the Sponsor and the Division should work closely together to try to find the sub-population of severe hypogonadotropic hypogonadal women who would benefit from treatment with Luveris™. The clinical review team recommends that any new Phase 3 trial look at the percentage of subjects ovulating as the primary efficacy endpoint, be a dose ranging study and evaluate a dose of Luveris™ lower than 75 IU/day (50 or 25 IU/day) in addition to the 75 IU/day dose. In addition the study should be conducted in the manner that this drug might be used in clinical practice allowing the FSH to be titrated with a fixed dose of Luveris™.

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

cc: Division File NDA 21-322
D. Shames, MD
A. Gassman, MD
K. Meaker.
A. Reddy
S. Slaughter, M.D., Ph.D.

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/s/

Shelley Slaughter
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MEDICAL OFFICER

DRAFT

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**Luveris™
Acting Deputy Division Director
Team Leader Review**

NDA: 21-322

Drug: Luveris™ (recombinant human Luteinizing Hormone [r-hLH])

Indication: Concomitant administration along with recombinant human follicle stimulating hormone (r-hFSH) for the induction of ovulation in infertile women with severe LH (< 1.2) ζ deficiency.

Dosage/Form/Route: 75 IU sterile lyophilized powder to be reconstituted with 1 ml Sterile Water for Injection. A single 75 IU dose is administered via subcutaneous injection once daily until estradiol and ultrasound monitoring indicate ζ hCG should be given to complete follicular development and effect ovulation. FSH should be administered concomitantly with Luveris™

Applicant: Serono Laboratories, Inc
Original Submission Date: May 1, 2001
Primary Review Completed: February 19 2002
Date of Memorandum: February 25, 2002

Background

With this application Serono is seeking approval for the indication of induction of ovulation in hypogonadotropic hypogonadal infertile women with severe LH (< 1.2) ζ deficiency. 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. 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 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 luteinizing hormone (rhLH).

Hypogonadotropic hypogonadism is a rare disorder of reproductive function that occurs in both males and females. In both sexes, the dysfunction is characterized by altered or absent hypothalamic-pituitary secretory activity resulting in arrested or attenuated gonadal function. Hypogonadotropic hypogonadism is classified as Group I anovulation in the World Health Organization (WHO) definitional classification of anovulation. Hypogonadotropic hypogonadism can be either a primary (congenital) or a secondary (acquired) disorder. Primary hypogonadotropic hypogonadism in women, as in men, can present in adolescence with the failure to develop secondary sexual characteristics. However, the clinical features often vary

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widely, with secondary sexual characteristics ranging from eunuchoidal features to moderate breast development. Amenorrhea (either primary or secondary) is often the presentation of females with hypogonadotropic hypogonadism. The estimated occurrence in females is one in 25,000. The Sponsor estimates that fewer than 700 women seek evaluation for infertility annually. Diagnosis of WHO Group I anovulatory patients relies on the history, documentation of anovulation in association with normal internal and external genitalia on physical or radiological examination, and laboratory confirmation of low or unmeasurable serum gonadotropin and estradiol levels. WHO Group I anovulatory subjects do not respond with withdrawal bleeding when a progestational agent is administered (progesterone challenge test). Treatment of infertility in hypogonadotropic hypogonadal women requires (re)institution of folliculogenesis (follicular recruitment, follicular growth and ovulation).

The process of folliculogenesis in the normal menstrual cycle relies on the appropriate and complex actions and interactions of the gonadotropins LH and FSH. The bulk of the scientific knowledge regarding follicular growth and development is based on non-primate models. The initiation of follicular growth is thought to be independent of gonadotropins. Gonadotropin-independent growth is limited and rapidly followed by atresia, if not rescued by gonadotropin. Beyond the gonadotropin-independent phase, follicular growth and development is primarily dependent on FSH. A decline in steroidogenesis in the late luteal phase allows a rise in FSH which results in the up-regulation (induction) of its own receptors on the plasma membrane of granulosa cells thus leading to FSH initiated aromatization (estradiol production) in these cells. FSH and estradiol work in concert to promote rapid accumulation of FSH receptors on the membranes of granulosa cells and proliferation of granulosa cells and production of estrogen. In human pre-antral and early antral follicles, LH receptors are present only on the theca cells (outer cell layer of the follicle organized from the stroma) and FSH receptors are only on granulosa cells. Ovarian steroidogenesis is always LH dependent. While it is generally agreed that some LH is necessary for appropriate follicular development, it is not known with certainty what level of endogenous LH is necessary to accomplish this. Women who have had their endogenous gonadotropins suppressed by pituitary suppression with gonadotropin-releasing hormone agonist successfully respond with follicular development and appropriate steroidogenesis when treated with exogenous FSH alone. A minimal amount of LH may be necessary and sufficient, because of paracrine cooperativity of ovarian growth modulators with FSH, to ensure adequate androgen production.

The creation of an estrogen rich and dominant microenvironment marks the follicle destined to ovulate. This follicle then directs its own fate with appropriate negative and positive feedback action on the pituitary. FSH working in concert with estrogen, induces LH receptors production on the plasma membrane of the antral follicle. When estrogen production by the preovulatory follicle becomes sufficient, a peripheral threshold concentration of estrogen is achieved which triggers a LH surge (positive feedback of estrogen on the pituitary). Final follicular maturation is accomplished under the primary influence of LH. In women who are administered exogenous FSH for ovulation induction, final follicular development and ovulation is accomplished by the administration of hCG, which has LH-like activity. The LH surge stimulates completion of reduction division in the oocyte, luteinization of the granulosa, and synthesis of progesterone and prostaglandins within the follicle. Progesterone enhances the activity of proteolytic enzymes responsible, together with prostaglandins, for digestion and rupture of the follicular wall. The midcycle rise in FSH (influenced by progesterone) frees the oocyte from follicular attachments and ensures that sufficient LH receptors are present to allow a normal luteal phase.

The Sponsor proposes that Luveris™ (r-hLH) administered with r-hFSH will induce adequate follicular development and ovulation in women with severe hypogonadotropic hypogonadism

(LH < 1.2) with infertility. Serono proposes that treatment with Luveris™ and Gonal-F® (r-hFSH) will be a benefit to these women beyond that provided by Gonal-F® alone. In support of this NDA application, Serono has submitted one Phase 3 trial and four supportive Phase 2 trials.

Regulatory History:

At the May 21, 1992 pre-IND meeting for this drug product, it was agreed that the Sponsor would conduct two identical Phase 2 dose finding trials, one in the U.S. (Protocol 6905) and one in Europe (Protocol 6253), in WHO Group I subjects. These two studies would serve as the principle studies supporting an application for ovulation induction in hypogonadotropic hypogonadal women seeking pregnancy. IND 44,108 was submitted December 8, 1993 with only the protocol for the U.S. study, Protocol 6905. The protocol was amended July 20, 1994 with changes to the enrollment criteria. The sponsor deleted the requirement for a negative progesterone challenge test and replaced it with the requirement for an estrogen level less than 60 pg/ml. FSH and LH requirement which had each been below 5 IU/L were change to be at or below the 50th percentile of normal range for the follicular phase established by the central laboratory, 10.85 IU/L and 13.3 IU/L for FSH and LH, respectively. Study 6905 started July 1994. The IND did not include the protocol for the European study and this protocol was not submitted to the Agency for review prior to the completion of this study.

Orphan Drug designation was granted on October 7, 1994.

Study 6253, the European study, enrolled only subjects with a screening LH of < 1.2 IU/L. Therefore, the sub-populations of women with hypogonadotropic hypogonadism based on endogenous LH levels was different for the two studies even though the pre-IND agreement was that the two studies would be identical. Study 6253 began September 1993. The primary endpoint for both studies was follicular development which was defined by three parameters (appropriate estradiol level, follicle of appropriate size [present on ultrasound] and a midluteal progesterone level indicative of ovulation), all of which had to be satisfied. Of note, even though both studies were initially supposed to be identical, the hormone levels used to define success for the co- primary efficacy parameters were different for the two studies.

The Sponsor stated in the first annual report to the IND, May 15, 1996, that the U.S. study would be the primary safety and efficacy study to support the NDA, while the European study would be supportive. The Sponsor's intention to have Study 6905 be the pivotal trial and the basis for the NDA was reiterated in the second annual report submitted May 16, 1997.

The Sponsor requested a pre-NDA meeting and submitted a briefing document for that meeting on June 12, 1998. The Sponsor requested that the Agency confirm that the data from Studies 6905 and 6253 were adequate for filing and approval of an NDA for the treatment of women with chronic anovulation due to hypogonadotropic hypogonadism. The briefing document now referred to study 6253 as the pivotal study to support the NDA. Only studies 6253 and 6905 were submitted as part of the briefing packet for the pre-NDA meeting. According to the Sponsor's analyses of the data (38 subjects) submitted to the briefing document for Study 6253, 75 IU of Luveris™ was numerically better than 25 IU of Luveris™ and placebo in follicular development in women with hypogonadotropic hypogonadism whose LH was \leq 1.2 IU/L. According to the Sponsor's analyses of the data submitted to the briefing document for Study 6905 (40 subjects), placebo, 25 IU of Luveris™ and 75 IU of Luveris™ were all effective in follicular development of women with hypogonadotropic hypogonadism whose LH was \leq 13.3 IU/L. A subset analysis of women (15 subjects) with LH < 1.2 in Study 6905 failed to confirm the findings of Study 6253.

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On July 10, 1998 a teleconference with the Sponsor was held to discuss the briefing package for the Pre-NDA meeting. The applicant was asked to submit an ITT analysis separately for Study 6253, Study 6905 and low LH (<1.2) subgroup for Study 6905 and an ITT analysis which integrated subjects from Study 6253 and the low LH subjects in 6905. These analyses were submitted in an addendum, dated July 27, 1998, to the Pre-NDA briefing package

On August 11, 1998, a teleconference was held with the Sponsor and the following FDA conclusions were discussed:

- *Studies 6253 and 6905 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*
- *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 6253*
- *Study 6905 showed the drug to be ineffective*
- *Although both Study 6905 and Study 6253 were designed as dose-finding studies, the studies made different dosing conclusions when the low LH patients were separated out*
 - *Study 6253 indicated that the dose should be started at 75 IU and titrated to 225 IU*
 - *In Study 6905, 80% of subjects responded to the 25 IU dose when only low LH patients were evaluated*
- *The effect of the drug in Study 6905 may have been masked by the broader inclusion criteria used in recruitment that were recommended by the Sponsor's investigators*
- *More data would be needed before the NDA was fileable*

In a follow-up communication dated September 4, 1998, the Sponsor restated their position that the data from Studies 6905 and 6253 supported the filing of the NDA for the proposed orphan indication and the intended patient population. At this time the Sponsor was now identifying Study 6253 as the pivotal study and Study 6905 as supportive

The fileability of the proposed NDA was discussed with CDER upper management (Deputy Director Center for Drug Evaluation and Research and Director of Office of Drug Evaluation [ODE] II) on October 21, 1998, and it was agreed that if the NDA was submitted, it would not be fileable.

On November 18, 1998, the Sponsor informed the Division in a supplemental pre-NDA briefing package of new data from two additional clinical trials conducted in Europe. Study 7798 was conducted in Germany in hypogonadotropic hypogonadal women with a LH < 1.2 and Study 8297 was conducted in Spain in hypogonadotropic hypogonadal women with LH below or within normal range. Both of these studies were conducted with doses of Luveris™ ≥ 75 IU/L.

The Deputy Director of ODE II and the Division met again with Serono on November 30, 1998. Included in the discussion from the Division were the following points.

- *Two dose finding studies using the same protocol were originally proposed at the pre-IND meeting; neither Study 6905 or 6253 were initially designated as pivotal trials*
- *Studies 6905 and 6253 were not powered on any criteria other than the limited size of the patient population*
- *A 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 test to be exploratory test and not significant for a pivotal trial*
- *The European study (6253) is significantly different from the U.S. Study (6905)*

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- *Studies 6253 and 6905 were designed as dose-finding studies and no hypothesis was set for the studies at the outset; additionally exploratory analyses (trend tests) were used to detect significance*
- *The data from Studies 6905 and 6253 can be used to make exploratory conclusions for further research; however, making efficacy conclusions based on these analyses is problematic*

Serono reiterated its position that 75 IU dose was chosen because it was optimal. The Sponsor was told that if the application was filed it could be taken to an advisory committee meeting

Further communication from Serono on December 16, 1998 clarified that Study 6253 and Study 7798 would form the basis of their proposed NDA.

On February 23, 1999, a teleconference was held with Serono to once again discuss the fileability of their proposed NDA. The following discussion and decisions were made in that teleconference.

- *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 refuse-to-file procedure, should it be submitted*
- *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™*
 - *All patients who are enrolled in the study should desire pregnancy as an outcome*
 - *A Phase 3 trial comparing the 75 IU dose to placebo should be performed; patients with LH levels < 5 IU could be enrolled; a significant subset of patients with LH level < 1.2 should also be included*
- *The primary clinical endpoint should be ovulation rate 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*
- *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*
- *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 calculation, the primary endpoints and the definition of success should be included in the proposal.*

Protocol IMP 21008 for a Phase 3 clinical trial was submitted to the IND on March 22, 1999. The following comments on that protocol were conveyed to the Sponsor in a teleconference held May 3, 1999.

- *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*
- *A 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 10 ng/mL for progesterone level should be considered 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.*

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Decisions reached were:

- *The Sponsor will attempt to blind the study as much as possible and resubmit the protocol, a justification or rationale as to why blinding is so difficult for this study should be submitted in the revised 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 rate and the addition of a placebo arm should be recalculated*

NDA 21-322 was received May 1, 2000. It was filed on June 30, 2001.

Clinical Efficacy and Safety

Study 21008 (multinational)

Study 21008 was a randomized, double blind, placebo-controlled, multi-center study conducted in 25 centers throughout the U.S., Canada, Israel and Australia. Subjects were randomized in a 2:1 design to receive 75 IU/day Luveris™ (r-hLH) and 150 IU/day Gonol-F® (r-hFSH) or placebo and 150 IU/day Gonol-F®. Women ages 18 to 39 with hypogonadotropic hypogonadism and who desired pregnancy were enrolled. These women were required to have on entrance, serum LH < 1.2 IU/L, serum FSH < 5 IU/L and serum E₂ < 60 pg/ml. It was required that the entrance endovaginal ultrasound show no clinically significant uterine abnormality, no ovarian tumor or cyst and ≤ to 13 follicles with diameter ≤ 13mm. Subjects with a history of ovarian hyperstimulation syndrome (OHSS) were excluded from the trial. A total of 39 subjects were randomized.

One cycle of treatment was evaluated. The primary efficacy endpoint was achievement of adequate follicular development as defined by the following three criteria, all of which should be satisfied.

1. At least one follicle ≥ 17 mm
2. Serum E₂ level ≥ 109 pg/mL (400 pmol/mL) on the day of hCG
3. Mid-luteal phase P₄ ≥ 7.9 ng/mL (25 nmol/L)

The Division had made a strong recommendation to the Sponsor that only ovulation rate (as determined by the percentage of subjects achieving a mid-luteal progesterone level ≥ 10 ng/ml) be used as the primary efficacy endpoint. It was further indicated to the Sponsor that the secondary variable of pregnancy rate would also be carefully considered. The Sponsor chose not to follow the Division's recommendation in the designation of the primary endpoint evaluated.

Efficacy analyses are shown in Table 1 and 2. The Sponsor's efficacy analysis (see Table 1 [from Statistical reviewer's Table 2]) used an evaluable patient population and counted as success, women who had their cycle cancelled for risk of OHSS. Of note, the clinical review found it objectionable to include as a success, a cancelled (no hCG given) ovulation induction cycle. Physicians treating infertility and, most importantly, women receiving infertility services would not consider the cancellation of a cycle to avoid an adverse outcome as a successful outcome of a therapy given for the purpose of achieving pregnancy and having a baby.

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Table 1
Evaluable Subjects (Sponsor's Analyses), Study 21008

	Placebo (n=10)	75 IU Luveris™ (n=24)
Primary Efficacy Variable		
Follicular development		
Success – n (%)	2 (20%)	16 (67%)
Failure – n (%)	8 (80%)	8 (33%)
p-value ^a = 0.023		
Secondary Efficacy Variable		
Follicle Size		
At least one follicle ≥ 17mm		
Success – n (%)	4 (40%)	15 (63%)
Failure – n (%)	6 (60%)	9 (38%)
Pre-Ovulatory E ₂ level ≥ 109 pg/mL		
Success – n (%)	2 (20%)	16 (67%)
Failure – n (%)	8 (80%)	8 (33%)
Midluteal P ₄ ≥ 7.9 ng/mL		
Success – n (%)	2 (20%)	12 (50%)
Failure – n (%)	8 (80%)	12 (50%)
Clinical Pregnancy		
Success – n (%)	1 (10%)	1 (4%)
Failure – n (%)	9 (90%)	23 (96%)
Risk of OHSS		
Yes – n (%)	1 (10%)	5 (21%)
No – n (%)	9 (90%)	19 (79%)

^aFisher's Exact Test

The Statistical reviewer's analysis of the ITT population is shown in Table 2 (from the Statistical reviewer's Table 4). At the request of the Clinical reviewer, the Statistical reviewer performed the ITT analysis counting as failures subjects whose cycles were cancelled because of risk of OHSS.

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Table 2

ITT Subjects (Statistical Reviewer's Analyses), Study 21008

	Placebo (n=13)	75 IU Luveris™ (n=26)
Primary Efficacy Variable (Subjects at risk for OHSS counted as success) Follicular Development Success – n (%) Failure – n (%) p-value ^a =0.008	2 (15%) 11 (85%)	16 (65%) 10 (35%)
Primary Efficacy Variable (Subjects at risk for OHSS <u>not</u> counted as success) Follicular Development Success – n (%) Failure – n (%) p-value ^a = 0.063	1 (8%) 12 (92%)	10 (38%) 16 (62%)
Secondary Efficacy Variables		
Follicle Size At least one follicle ≥ 17mm Success – n (%) Failure – n (%)	4 (31%) 9 (69%)	16 (62%) 10 (38%)
Pre-Ovulatory E₂ level ≥ 109 pg/mL Success – n (%) Failure – n (%)	2 (15%) 11 (85%)	16 (62%) 10 (38%)
Midluteal P₄ ≥ 7.9 ng/mL Success – n (%) Failure – n (%) p-value ^a = 0.083	2 (15%) 11 (85%)	12 (46%) 14 (54%)
Clinical Pregnancy Success – n (%) Failure – n (%)	1 (8%) 12 (92%)	1 (4%) 25 (96%)
Risk of OHSS Yes – n (%) No – n (%)	1 (8%) 12 (92%)	6 (23%) 20 (77%)

^aFisher's Exact Test

When the risk of OHSS is not counted as a success the p-value changes from 0.008 to 0.063 and the difference between treatment with Luveris and treatment with placebo is no longer statistically significant. In this analysis of the Statistical reviewer which was utilized by the clinical team to determine efficacy, treatment with the 75 IU/day dose of Luveris™ is not efficacious.

No subjects died during the course of this 1 cycle study. One subject terminated the study prematurely after 4 days due to a rash. A total of 44 adverse events were recorded in 13 subjects (33%). The majority of the adverse events were mild or moderate. One adverse events was

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judged to be severe; this being OHSS in a subject who had been given placebo. This event was not classified as serious by the investigator. The incidence of OHSS in all treated subjects was 2.6%. Of those 7 subjects whose cycles were cancelled for the risk of OHSS, 1 (14.3%) developed the syndrome. One serious adverse event was recorded. This occurred in a subject, given placebo, who prematurely delivered twins via Cesarean section at 24-weeks gestation. Subsequent to delivery, one of the twins (A, weight 636 g) was diagnosed as septic with E. Coli and developed complications including intracerebral hemorrhage. The infant died after being removed from life support.

No major safety concerns were seen with the 75 IU/day dose of Luveris™. However when one considers the overall benefit to potential risk profile it is not favorable. Twenty-three percent (23%) of the cycles with 75 IU/day dose of Luveris™ were cancelled for risk of OHSS and when these subjects were appropriately included in the ITT analysis as failures, this dose failed to demonstrate efficacy (a statistical difference from placebo).

Study 6253 (Europe)

Study 6253 was an open label, randomized, dose-finding, multi-center (10) study conducted in Europe and Israel to determine the minimum 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). Subjects were randomized in a 1:1:1:1 basis to Luveris™ 25, 75, or 225 IU/day or placebo and 150 IU/day r-hFSH. Women aged 18 to 35 with hypogonadotropic hypogonadism, were eligible. Volunteers did not necessarily desire pregnancy. These women were required to have on entrance serum LH < 1.2 IU/L and serum FSH < 5 IU/L. It was required that the entrance ultrasound show a uterus with a midline echo, no ovarian tumor or cyst and ≤ to 13 (endovaginal probe) or 10 (abdominal) small follicles on the largest section through each ovary. Subjects with a history of OHSS were excluded from the trial. Subjects were to use mechanical contraception if not wishing to conceive. A total of 38 subjects were randomized

Subjects received treatment for up to 3 cycles for a total of 53 cycles (39 cycle A, 9 cycle B and 5 cycle C). Only cycle A of treatment was evaluated. The primary efficacy endpoint was follicular development as defined by the following three criteria, all of which were to be satisfied.

1. At least one follicle ≥ 17 mm
2. Serum E₂ level ≥ 400 pmol/L on the day of hCG
3. Mid-luteal phase P₄ ≥ 25 nmol/L

Pregnancy was considered as a secondary outcome. Study 6253 was the only one of the four supporting studies submitted that had the same population of hypogonadotropic hypogonadal women (i.e. LH < 1.2) and the same criteria for the primary efficacy endpoint as the pivotal study, Study 21008.

Efficacy analyses are shown in Table 3 and 4. The Sponsor's efficacy analysis (see Table 3 [from Statistical reviewer's Table 5]) used the ITT patient population of all patients randomized who received at least one dose of treatment. The analysis counted as success, women who had their cycle cancelled for risk of ovarian hyperstimulation syndrome (OHSS). The sponsor performed a Cochran-Armitage trend test using all four dose groups. The Statistical reviewer commented that this analysis was appropriate for a dose-finding study (not the case for pivotal Phase 3 efficacy), but in the analysis presented by the Sponsor weights of (-2, 0, 1, 1) were applied. This analysis gave no weight to the 25 IU/day group and equal weight to the 75 and 225 IU/day groups. A between group test of the Luveris™ 75 IU/day group vs. placebo had not been originally planned.

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Table 3
ITT Subjects (Sponsor's Analyses), Study 6253

	Placebo (n=9)	25 IU Luveris™ (n=8)	75 IU Luveris™ (n=11)	225 IU Luveris™ (n=10)
Primary Efficacy Variable				
Follicular development				
Success – n (%)	1 (11%)	2 (25%)	7 (64%)	7 (70%)
Failure – n (%)	8 (89%)	6 (75%)	4 (36%)	3 (30%)
p-value = 0.004 (Trend test)				
Secondary Efficacy Variable				
Follicle Size				
At least one follicle ≥ 17mm				
Success – n (%)	2 (22%)	4 (50%)	7 (64%)	4(40%)
Failure – n (%)	7 (78%)	4 (50%)	4 (36%)	6(60%)
Pre-Ovulatory E ₂ level ≥ 400 pmol/L				
Success – n (%)	1 (11%)	2 (25%)	6 (55%)	5 (50%)
Failure - n (%)	8 (89%)	6 (75%)	5 (45%)	5 (50%)
Midluteal P ₄ ≥ 25 nmol/L				
Success – n (%)	1 (11%)	2 (25%)	5 (45%)	5 (50%)
Failure – n (%)	8 (89%)	6 (75%)	6 (55%)	5 (50%)
Clinical Pregnancy				
N = subjects desiring pregnancy	7	6	9	6
Success – n (%)	0 (0%)	0 (0%)	2 (22%)	0 (0%)
Failure - n (%)	7 (100%)	6 (100%)	7 (78%)	6 (100%)
Risk of OHSS				
Yes – n (%)	0 (0%)	0 (0%)	2 (18%)	3 (30%)
No – n (%)	9 (100%)	8 (100%)	9 (42%)	7 (70%)

The Statistical reviewer's analysis of the ITT population is shown in Table 4 (from the Statistical reviewer's Table 7). At the request of the Clinical reviewer, the Statistical reviewer performed the ITT analysis counting as failures subjects whose cycles were cancelled because of risk of OHSS. Although pairwise comparisons had not been planned per protocol, the Statistical reviewer used the Fisher's exact test to compare the 75 IU/day Luveris™ group to the placebo group to indicate how strongly these results supported the efficacy of the 75 IU/day dose.

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Table 4
ITT Subjects (Statistical Reviewer's Analyses), Study 6253

	Placebo (n=9)	25 IU Luveris™ (n=8)	75 IU Luveris™ (n=11)	225 IU Luveris™ (n=10)
Primary Efficacy Variable (Subjects at risk for OHSS counted as success) Follicular Development Success – n (%) Failure – n (%) p-value vs. placebo ^a	1 (11%) 8 (89%)	2 (25%) 6 (75%)	7 (64%) 4 (36%) 0.028	7 (70%) 3 (30%)
Primary Efficacy Variable (Subjects at risk for OHSS <u>not</u> counted as success) Follicular Development Success – n (%) Failure – n (%) p-value vs. placebo ^a	1 (11%) 8 (89%)	2 (25%) 6 (75%)	5 (45%) 6 (55%) 0.157	4 (40%) 6 (60%)
Follicle Size At least one follicle ≥ 17mm Success – n (%) Failure – n (%)	2 (22%) 7 (78%)	4 (50%) 4 (50%)	6 (55%) 5 (45%)	4 (40%) 6 (60%)
Pre-Ovulatory E ₂ level ≥ 400 pmol/L Success – n (%) Failure – n (%)	1 (11%) 8 (89%)	2 (25%) 6 (75%)	6 (55%) 5 (45%)	5 (50%) 5 (50%)
Midluteal P ₄ ≥ 25 nmol/L Success – n (%) Failure – n (%)	1 (11%) 8 (89%)	2 (25%) 6 (75%)	5 (45%) 6 (55%)	5 (50%) 5 (50%)
Clinical Pregnancy N = subjects desiring pregnancy Success – n (%) Failure – n (%)	7 0 (0%) 7 (100%)	6 0 (0%) 6 (100%)	9 2 (22%) 7 (78%)	6 0 (0%) 6 (100%)
Risk of OHSS Yes – n (%) No – n (%)	0 (0%) 9 (100%)	0 (0%) 8 (100%)	2 (18%) 9 (42%)	3 (30%) 7 (70%)

^aFisher's Exact Test

The Sponsor used Study 6253 to select the 75 IU/day dose. When subjects who were withdrawn for risk of OHSS are counted as successes, the 75 IU/day dose of Luveris™ is statistically different from placebo. When subjects whose cycles were cancelled for risk of OHSS are considered as treatment failures (see discussion above), there is not sufficient evidence to support a statistical difference from placebo. Therefore, this study does not provide supportive evidence for the efficacy of the 75IU/day dose of Luveris™.

No subjects died during the course of this study. No discontinuations due to adverse events occurred. A total of 42 adverse events occurred in 14 of the 53 cycles. The majority of the adverse events were reported in cycles not treated with r-hLH. Two serious adverse events occurred, one subject had a miscarriage and one subject was involved in an automobile accident.

Study 6905 (United States)

Study 6905 was an open label, randomized, dose-finding, multi-center (14 centers) study conducted in the United States to determine the minimum effective dose and assess the safety of r-hLH to support the r-hFSH induced follicular development in anovulatory women with hypogonadotropic hypogonadism. Subjects were randomized in a 1:1:1:1 basis to Luveris™ 25, 75, or 225 IU/day or placebo and 150 IU/day Gonal-F®. Women aged 18 to 40 with hypogonadotropic hypogonadism were eligible. Volunteers did not necessarily desire pregnancy. These women were required to have on entrance, serum LH \leq 13.3 IU/L and serum FSH \leq 10.85 IU/L. It was required that the entrance ultrasound show a normal uterus, no ovarian tumor or cyst and \leq to 13 follicles on the largest section through each ovary. Subjects with a history of OHSS were excluded from the trial. Subjects were to use mechanical contraception if not wishing to conceive. A total of 43 subjects were randomized. Three subjects were randomized but not treated.

Subjects received treatment for up to 3 cycles for a total of 61 cycles (40 cycle A, 16 cycle B and 5 cycle C). Only cycle A of treatment was evaluated. The primary efficacy endpoint was follicular development as defined by the following three criteria, all of which were to be satisfied.

4. At least one follicle \geq 17 mm
5. Serum E₂ level \geq 160 pg/mL on the day of hCG
6. Mid-luteal phase P₄ \geq 10 ng/mL

Pregnancy was considered as a secondary outcome.

Efficacy analyses are shown in Table 5 and 6. The Sponsor's efficacy analysis (see Table 5 [from Statistical reviewer's Table 8]) used the patient population of all patients randomized who received at least one dose of treatment (All Treated). The analysis counted as success, women who had their cycle cancelled for risk of OHSS. The sponsor performed a Cochran-Armitage trend test using all four dose groups. The Statistical reviewer commented that this analysis was appropriate for a dose-finding study, but in the analysis presented by the Sponsor weights of (-2, 0, 1, 1) were applied. This analysis gave no weight to the 25 IU group. The 75 and 225 IU/day groups were combined for the test. Therefore, the results do not adequately represent the 75 IU/day dose for which the Sponsor is requesting consideration.

Table 5
ITT Subjects (Sponsor's Analyses), Study 6905

	Placebo (n=11)	25 IU Luveris™ (n=9)	75 IU Luveris™ (n=11)	225 IU Luveris™ (n=9)
Primary Efficacy Variable				
Follicular development				
Success – n (%)	7 (64%)	9 (100%)	8 (73%)	6 (67%)
Failure – n (%)	4 (36%)	0 (0%)	3 (27%)	3 (33%)
p-value = 0.774 (Trend test)				
Secondary Efficacy Variable				
Follicle Size				
At least one follicle ≥ 17mm				
Success – n (%)	10 (91%)	9 (100%)	11 (100%)	7 (78%)
Failure – n (%)	1 (9%)	0 (0%)	0 (0%)	2 (22%)
Pre-Ovulatory E ₂ level ≥ 160 pg/mL				
Success – n (%)	7 (64%)	9 (100%)	9 (82%)	6 (67%)
Failure – n (%)	4 (36%)	0 (0%)	2 (18%)	3 (33%)
Midluteal P ₄ ≥ 10 ng/mL				
Success – n (%)	10 (91%)	9 (100%)	9 (82%)	7 (78%)
Failure – n (%)	1 (9%)	0 (0%)	2 (18%)	2 (22%)
Clinical Pregnancy				
N = subjects desiring pregnancy	10	8	10	6
Success – n (%)	2 (20%)	1 (13%)	3 (30%)	2 (33%)
Failure – n (%)	8 (80%)	7 (88%)	7 (70%)	4 (67%)
Risk of OHSS				
Yes – n (%)	2 (18%)	2 (22%)	1 (9%)	0 (0%)
No – n (%)	9 (82%)	7 (78%)	10 (91%)	9 (100%)

The Statistical reviewer's analysis of the ITT population is shown in Table 6 (from the Statistical reviewer's Table 10). At the request of the Clinical reviewer, the Statistical reviewer performed the ITT analysis counting as failures subjects whose cycles were cancelled because of risk of OHSS.

Table 6
ITT Subjects (Statistical Reviewer's Analyses), Study 6905

	Placebo (n=11)	25 IU Luveris™ (n=9)	75 IU Luveris™ (n=11)	225 IU Luveris™ (n=90)
Primary Efficacy Variable (Subjects at risk for OHSS counted as success) Follicular Development				
Success – n (%)	7 (64%)	9 (100%)	8 (73%)	6 (67%)
Failure – n (%)	4 (36%)	0 (0%)	3 (27%)	3 (33%)
Primary Efficacy Variable (Subjects at risk for OHSS <u>not</u> counted as success) Follicular Development				
Success – n (%)	5 (45%)	7 (78%)	7 (64%)	6 (67%)
Failure – n (%)	6 (55%)	2 (22%)	4 (36%)	3 (33%)
Follicle Size At least one follicle ≥ 17mm				
Success – n (%)	8 (73%)	7 (78%)	10 (91%)	7 (78%)
Failure – n (%)	3 (27%)	2 (22%)	1 (9%)	2 (22%)
Pre-Ovulatory E₂ level ≥ 160 pg/mL				
Success – n (%)	5 (45%)	7 (78%)	8 (73%)	6 (67%)
Failure – n (%)	6 (55%)	2 (22%)	3 (27%)	3 (33%)
Midluteal P₄ ≥ 10 ng/mL				
Success – n (%)	8 (73%)	7 (78%)	8 (73%)	7 (78%)
Failure – n (%)	3 (27%)	2 (22%)	3 (27%)	2 (22%)
Clinical Pregnancy N = subjects desiring pregnancy	10	8	10	6
Success – n (%)	2 (20%)	1 (13%)	3 (30%)	2 (33%)
Failure – n (%)	8 (80%)	7 (88%)	7 (70%)	4 (67%)
Risk of OHSS				
Yes – n (%)	2 (18%)	2 (22%)	1 (9%)	0 (0%)
No – n (%)	9 (82%)	7 (78%)	10 (91%)	9 (100%)

^aFisher's Exact Test

The Sponsor's trend testing, with subjects whose cycles had been cancelled for risk of OHSS counted as success, shows no statistically significant trend for any dose of Luveris™ in this population of hypogonadotropic hypogonadal women with a broader inclusion based on serum LH levels. As stated previously, since the 75 IU/day and the 225 IU/day dose were combined for

the statistical testing, the results do not adequately represent the 75 IU/day dose. When cancellation of a cycle for risk of OHSS is considered a failure, differences in the Luveris™ doses and placebo are still not evident.

For consistency with the LH < 1.2 study population in Study 21008 and Study 6253 (the population of hypogonadotropic hypogonadal women now identified by the Sponsor as the population sought for approval), the Statistical reviewer performed a subgroup analysis of subjects with LH < 1.2 on the data from Study 6905, Table 7 (from Statistical reviewer's Table 13).

Table 7
ITT Subjects; LH < 1.2

	Placebo (n=3)	25 IU Luveris™ (n=5)	75 IU Luveris™ (n=3)	225 IU Luveris™ (n=4)
Primary Efficacy Variable (Subjects at risk for OHSS counted as success)				
Follicular Development				
Success – n (%)	0 (0%)	5 (100%)	2 (67%)	3 (75%)
Failure – n (%)	3 (100%)	0 (0%)	1 (33%)	1 (25%)
Primary Efficacy Variable (Subjects at risk for OHSS <u>not</u> counted as success)				
Follicular Development				
Success – n (%)	0 (0%)	4 (80%)	2 (67%)	3 (75%)
Failure – n (%)	3 (100%)	1 (20%)	1 (33%)	1 (25%)
Risk of OHSS				
Yes – n (%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)
No – n (%)	3 (100%)	4 (80%)	3 (100%)	4 (100%)

The subgroup analysis is based on very small numbers and caution must be exercised in drawing conclusions from data on such a small number of subjects. Applying only a numerical consideration, the analysis is suggestive of a difference between Luveris™ vs. placebo but it does not support that the higher doses of Luveris™ are more effective than the 25 IU/day dose.

No deaths were reported in this study. There were no serious adverse events and no one discontinued the study due to adverse events. A total of 91 adverse events were reported

Study 7798

Study 7798 was an open label, randomized, dose-finding, crossover, multi-center (7 centers) study conducted in Germany. The goal of the study was to determine the efficacy and safety of r-hLH, administered subcutaneously at doses of 75, 150 or 225 IU/day (equal randomization on a 1:1:1 basis) to support stimulation of follicular development with a fixed dose of 150 IU/day of r-

hFSH in anovulatory women with hypogonadotropic hypogonadism. No dose lower than 75 IU/day was evaluated. Women aged 18 to 39 with hypogonadotropic hypogonadism and desiring pregnancy were eligible. These women were required to have on entrance a serum LH < 1.2 IU/L and a serum FSH < 5 IU/L. In addition subjects were required to have a negative progesterone challenge test or no adult reaction after GnRH testing. It was required that the entrance ultrasound show an endometrial thickness \leq 5mm, no ovarian tumor or cyst and \leq to 10 small follicles on the largest section through each ovary. Subjects with a history of OHSS were excluded from the trial. A total of 15 subjects were randomized. Fifteen subjects 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 subjects received 75 IU/day, 11 patients received the 150 IU/day and 10 received the 225 IU/day dose. Eight subjects withdrew prematurely from the study, 2 while being treated with the 75 IU/day dose, 5 while being treated with the 150 IU/day dose and 1 while being treated with the 225 IU/day doses. Reasons for withdrawal prior to the third cycle were 3 for pregnancy, 2 for OHSS (risk or actual syndrome), 1 for non-compliance, 1 for spontaneous pregnancy in a rest cycle and 1 for personal reasons.

The primary efficacy endpoint was follicular development as defined by the following three criteria, all of which were to be satisfied.

1. At least one follicle \geq 17 mm
2. Serum E₂ level \geq 200 pg/mL on the day of hCG
3. Mid-luteal phase P₄ \geq 10 ng/mL

The Sponsor's analysis of this study did not count as success, women who had their cycle cancelled for risk of OHSS. The Sponsor's ITT analysis showed follicular development in 20% of women treated with 75 IU/day of Luveris™, 0% of women treated with 150 IU/day of Luveris™ and 40% of subjects treated with 225 IU/day of Luveris™. No statistical conclusions were tested for this study.

No subject died during this 3 cycle study. Four serious adverse events, all OHSS and all requiring hospitalization, were reported in 3 subjects during this study. Two subjects were discontinued from the study because of OHSS. Four (26.7%) of the 15 subjects experienced at least one adverse event. All but one of these occurred in the first cycle of treatment.

Study 8297

Study 8297 was an open label, non-comparative, multi-center (14 centers) Phase 2 study conducted in Spain to evaluate the efficacy and safety of r-hLH to support r-hFSH-induced follicular development in LH and FSH deficient anovulatory women. In cycle 1, subjects received 75 IU/day of Luveris™ and 150 IU/day r-hFSH. If the subject experienced no follicular development in the first cycle, she could be treated with 150 IU/day Luveris™ in the second cycle and stepped-up to 225 IU/day Luveris™ in the third cycle. Women aged 18 to 35 with hypogonadotropic hypogonadism and desiring pregnancy were eligible. These women were required to have on entrance serum LH and serum FSH that were below or within the reference range. In addition, subjects were required to have a negative progesterone challenge test. It was required that the entrance ultrasound show a normal uterus, no ovarian tumor or cyst and \leq to 13 follicles on the largest section through each ovary. Subjects with a history of OHSS were excluded from the trial. A total of 38 subjects received study drug for up to 3 cycles for a total of 85 treatment cycles (38 Cycle A [75 IU/day], 29 Cycle B [150 IU/day] and 18 Cycle C [225 IU/day]).

The primary efficacy endpoint was follicular development as defined by the following two criteria, each of which were to be satisfied.

1. At least one follicle ≥ 18 mm
2. Mid-luteal phase $P_4 \geq 10$ 30 nmol/L

The Sponsor's analysis of this study included as success, women who had their cycle cancelled for risk of OHSS. The Sponsor's ITT analysis showed follicular development (as defined in the protocol) in 82% of women treated with 75 IU/day of Luveris™. When subjects who were withdrawn for risk of OHSS are not treated as success, follicular development (by the protocol defined 2 criteria) occurred in 55% of subjects. Women in this study were allowed to have gonadotropin levels at baseline that were in the normal range. Even though it is acknowledged that some women with hypogonadotropic hypogonadism may have LH levels that are within normal limits quantitatively by immunoassay, but biologically less active on bioassay, this population is different from that of the other 4 studies presented and may not be easily compared. In the subgroup analysis of subjects with LH less than 1.2 IU/L on baseline, follicular development occurred in 59% of subjects when subjects whose cycles were cancelled for the risk of OHSS are not included as success. No comparator group is available to assess the significance of this rate.

No subject died during this 3 cycle study. Five serious adverse events, two moderate cases of OHSS requiring hospitalization, one miscarriage and twins each with an inguinal hernia, were reported during this study. Two subjects were discontinued from the study because of OHSS. Four (26.7%) of the 15 subjects experienced at least one adverse event. All but one of these occurred in the first cycle of treatment.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

The evaluative report of the clinical inspections for NDA 21-322 summarized inspections at four clinical sites (Dr. Kaufmann-Mount Pleasant, South Carolina; Sr. Stadtmauer-Cary, North Carolina; Dr. Vaughn-Austin, Texas; and Dr. Yeko; Tampa, Florida) for Study 21008. All of these sites were given a VAI classification for minor deviations from regulations; Data acceptable. None of the findings on inspection at the sites of Drs. Stadtmauer and Vaugh were considered to adversely impact the acceptability of the study data generated at these sites. However, inspection of Dr. Kaufman revealed that he failed to adhere to the protocol inclusion criteria for the two subjects that he enrolled in this study and that he failed to maintain adequate/accurate records; there were inappropriate revisions noted in the study records, including the use of correction fluid, and a failure to identify the persons effecting the changes and the date of the revisions. Dr. Yeko was originally assessed to have violated protocol in the discontinuation of subjects at risk for OHSS. However, it was concluded that the discontinuations were consistent with the protocol. One subject at Dr. Yeko's site had not had a pregnancy test documented immediately prior to her initial stimulation and local laboratory reports were faxed copies rather than the original. Consideration of these minor deviations from regulation was made by the clinical reviewer and it was decided that none of these adversely affected the integrity of the data.

Clinical Pharmacology and Biopharmaceutics

The following is the summary of the Clinical Pharmacology and Biopharmaceutical review.

The Sponsor has submitted 3 pharmacokinetic (PK) studies to support the PK profile of Luveris™ following subcutaneous administration. The studies provide evidence of an acceptable PK profile for r-hLH.

None of the studies included accurate PK profile and parameter from the subcutaneous 75 IU dose (to-be-marketed product) due to fact that baseline LH levels interfered with the analysis form this dose. However, PK profiles from higher doses 150 and 300 IU/day were provided. There is no indication that the product that is to be marketed will have a PK profile that is unacceptable to support efficacy and safety.

The intended to-be-marketed formulation is *not* exactly the same as the clinical trial formulation. However, an adequate bioequivalence study was conducted and the results show that the two formulations are bioequivalent. Hence the change in formulations is acceptable and the new formulation may be marketed replacing the clinical trial formulation

At the conclusion of the review there were no outstanding Clinical Pharmacology and Biopharmaceutics issues. From the Office of Clinical Pharmacology and Biopharmaceutics perspective, the NDA is acceptable for approval.

Chemistry Manufacturing and Controls (CMC)

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

Luveris™ is a sterile, lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP. Each vial contains 82.5 IU lutropin alfa r-hLH, equivalent to 3.7 µg r-hLH and when reconstituted will deliver 75 IU (3.4 µg) of r-hLH. The vials are over-filled to compensate for losses during reconstitution and administration to the patient. The formulation contains 0.1 mg L-methionine [], 47.75 mg sucrose, 0.05 mg polysorbate 20, 0.825 mg disodium phosphate dihydrate, 0.052 mg sodium dihydrogen phosphate monohydrate, and phosphoric acid and/or sodium hydroxide to adjust the pH. The drug products is manufactured as a sterile solution, filled into [] glass vials and lyophilized to yield the final product as a white pellet. The vials are sealed a [] rubber stopper and capped by an aluminum seal ring and flip-off cap. All manufacturing operations and release testing for the drug product, except for the bioassay test, are conducted at Laboratoires Serono, S.A. (LSA) in Aubonne, Switzerland. The bioassay test is performed at [] The product quality from a microbiology point of view is acceptable. []

[] The proposed specifications were found to be acceptable in the CMC review.

The relevant DMFs for the glass vial and rubber stopper have been reviewed and determined to be adequate as a container/ closure system for this drug product. The Microbiology reviewer determined that the integrity of the container/closure system was acceptable. Based on the stability data provided, an 18-month expiry date could be granted, when stored at 25° C. Storage under refrigerated conditions is also acceptable since the product is contained in a sealed glass vial.

The drug substance-r-hLH is a heterodimer glycoprotein, composed of two non-covalently linked identical subunits, designate alpha and beta. Natural hLH glycans contain N-acetylgalactosamine residues and their sulfated derivatives while the r-hLH glycans contain only sialylated species. Standard recombinant DNA techniques were used to isolate and clone the alpha and beta subunit genes into expression vectors and transfect into a standard Chinese Hamster Ovary Cell line. During the production phase, [redacted]

J. These operations are conducted at Laboratoires Serono, S.A. (LSA) in Aubonne, Switzerland. Release testing, except for the bioassay testing, is also performed at the same site. The bioassay test is performed at [redacted]

J The proposed specifications are acceptable. The proposed specifications were determined to be acceptable after the CMC review. The Microbiology review determined that the NDA adequately addressed microbiology product quality and has recommended approval from a Microbiology standpoint.

At the conclusion of the review there were no pending approvability CMC issues. From a CMC viewpoint the product could be approved.

Product Name

The tradename Luveris™ was recommended for acceptance by OPDRA on November 27, 2001.

Pre-clinical Pharmacology and Toxicology

Based on the structural similarity of r-hLH to urinary-derived human LH and pituitary-derived human LH and the pre-clinical and clinical experience of the proposed formulation, Pharmacology considers Luveris™ safe for the proposed indication and recommends approval from a Pharmacology standpoint.

Discussion and Conclusions

The data collected in the pivotal Phase 3 trial, Study 21008, and the four supportive Phase 2 trials, Studies 6253, 6905, 7798 and 8297, do not provide sufficient evidence to support the efficacy of the 75 IU/day dose of Luveris™ in follicular development and ovulation induction in hypogonadotropic hypogonadal women with infertility. The benefit to risk profile of the 75 IU/day dose is not acceptable. In the only Phase 3 study, 23% of subjects on the 75 IU/day dose of Luveris™ had their cycle cancelled for the risk of OHSS. In the only supportive study with the same population (baseline LH < 1.2) and the same efficacy criteria as the Phase 3 trial, Study 6253, 18% of the subjects in the 75IU/day dose had their cycle canceled for risk of OHSS. In that same study 0% of subjects treated with 25 IU/day of Luveris™ had their cycle canceled for risk of OHSS. The integrated summary of safety review reveals that 21.7% of the 92 subjects treated with the 75 IU/day dose of Luveris™ had their ovulation induction cycle canceled for the risk of OHSS, while 11.8 % of subjects treated with 25IU/day of Luveris™ had treatment cycle cancellation for the risk of OHSS. The data from Study 21008, Study 6253 and the ISS review suggest that perhaps a lower dose of Luveris™ may possess a better benefit to risk profile in

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women with hypogonadotropic hypogonadism (and specifically in the women with baseline LH < 1.2).

I concur with the clinical reviewer and I recommend that this NDA not be approved. The Clinical team recommends that to address the deficiency, the Sponsor conduct a Phase 3 clinical trial that is appropriately powered to demonstrate whether Luveris™ doses are statistically different from placebo for ovulation induction in hypogonadotropic hypogonadal women with profound LH deficiency, as defined by a baseline LH level <1.2 IU/L. We further recommend that this new Phase 3 trial, with percentage of subjects ovulating as the primary efficacy endpoint, be a dose ranging study and that it evaluates a dose of Luveris™ lower than 75 IU/day (50 or 25 IU/day) in addition to the 75 IU/day dose.

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

cc: Division File NDA 21-239
D. Shames, MD
R. Bennett, MD
K. Meaker.
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S. Slaughter, M.D., Ph.D.

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 22, 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 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, τ

\mathcal{I} 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 luteinizing 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 I 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 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

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.

- 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

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- 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

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

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

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

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.

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

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.

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On Original*

Table 6

Follicular Development Rate (ITT) 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	1 (11%)	2 (25%)	5 (45%)
No	8 (89%)	6 (75%)	6 (55%)

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 patients 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 patients receiving 25 IU of Luveris™ had their treatment cycle cancelled because of the risk of ovarian hyperstimulation. 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.

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. The optimal trial

study would be a direct head-to-head comparison of r-hLH/r-hFSH versus menotropins. This recommendation by FDA to the sponsor was not implemented. Instead, the prime studies compared r-hLH/r-hFSH with placebo/r-hFSH which created a design/analysis conundrum as explained below.

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 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",

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

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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).

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 ovulatory 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 not 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.

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 LH \leq 13.3 IU/L; an ultrasound showing a normal uterus, no ovarian tumor cyst and less than or equal to 13 follicles on the largest section through each ovary; BMI between 18 and 35 kg/m², 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

LH < 1.2 IU/L). A statistically significant dose related benefit was observed (p=0.039).

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:

r-hLH Dose (IU/.day):

Sequence	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 E₂ level ≥ 200 pg/mL on the day of hCG administration, and a mid luteal phase P₄ 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 (E₂ < 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. 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 P₄ 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 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. 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).

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.

NDA 21-322
Luveris (lutropin alfa for injection) 75 I.U.
Serono, Inc.

Safety Update Review

The safety update is included in the Medical Officer Review dated February __, 2002.

MR
2/09/02

Appears This Way
On Original