CENTER FOR DRUG EVALUATION AND RESEARCH

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NDA 21-322

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-322
Name of drug:	Luveris (lutropin alfa for injection) 75 IU
Applicant:	Serono, Inc.
Indication:	Concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH and FSH deficiency
Documents reviewed:	Vol. 1.1, 1.2, 1.73-1.86
Project manager:	Archana Reddy (HFD-580)
Clinical reviewer:	Ridgely Bennett, M.D. (HFD-580)
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Statistical reviewer:	Kate Meaker, M.S. (HFD-715)
Statistics team leader:	Mike Welch, Ph.D. (HFD-715)
Biometrics division director:	Ed Nevius, Ph.D. (HFD-715)

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

The primary efficacy decision for the Luveris 75 IU dose focuses on a single placebo-controlled study (21008). The primary efficacy endpoint is follicular development. Based on the definition of follicular development from the protocol, the Luveris 75 IU dose is statistically different from placebo (p-value = 0.023).

The protocol defined patients who stopped treatment due to the risk of Ovarian Hyperstimulation Syndrome (OHSS) as treatment successes for follicular development, even though the ovulation cycle was stopped. The Medical Officer requested that I calculate the success rate for follicular development after reclassifying patients at risk for OHSS as treatment failures. Using the Medical Officer's classification, the Luveris 75 IU treatment group is only marginally statistically different from placebo (p-value = 0.063). The Medical Officer will address the clinical relevance of this latter result in his review.

Two Phase 2 dose-finding studies (6253 and 6905) were submitted as supportive evidence. Both were randomized, double-blind parallel-arm studies with 25, 75, and 225 IU Luveris dose groups along with a placebo control group. The results from study 6253 were similar to Study 21008 and supported the same conclusions regarding the Luveris 75 IU dose. However, study 6905 did not suggest a difference between the Luveris 75 IU treatment group and the placebo group.

Additional supportive evidence was provided from two other studies. Study 7798 was a small crossover study (n=5 per dose group) with no placebo control. Study 8297 was a single-arm study with 38 patients assigned to the Luveris 75 IU dose. These provide descriptive evidence only. No statistical conclusions can be drawn from these two studies.

The main issue regarding the efficacy decision is the appropriate classification of patients who stopped treatment, and therefore stopped the ovulation cycle, due to the risk of OHSS. If patients who stopped treatment due to a risk of OHSS are classified as treatment success for follicular development, then two of the three placebo-controlled clinical trials conclude Luveris 75 IU is statistically significantly different from placebo while the third study does not support this conclusion. However, if patients who stopped treatment due to a risk of OHSS are classified as treatment failures for follicular development, none of the studies support a statistically significant difference of Luveris 75 IU versus placebo. The final decision on that issue rests with the Medical Officers.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Luveris 75 IU is a recombinant human Luteinizing Hormone (r-hLH) to be administered by subcutaneous (SC) injection. The sponsor was granted orphan drug status for this IND (44,108) for a patient population of women with hypogonadotropic hypogonadism (HH). The patient population was defined as having a baseline LH level < 1.2 IU/L, along with other characteristics. The desired indication is ovulation induction in anovulatory women with HH.

A total of five clinical studies were included in the statistical review. A single Phase 3 study (21008) compared Luveris 75 IU to placebo. It was a randomized, double-blind study conducted in the U.S., Canada, Israel, and Australia. Two small Phase 2 randomized, double-blind, dose-finding studies (6253 and 6905) included treatment arms of 25, 75 or 225 IU Luveris, along with a placebo-control arm. Study 6253 was conducted in Europe, and study 6905 was conducted in the U.S. A small crossover study (7798) from Germany included Luveris doses of 75, 150 or 225 IU, but only had 5 patients per dose and no placebo arm. Lastly, study 8297 was a single-arm uncontrolled study conducted in Spain with 38 patients treated with Luveris 75 IU.

The sponsor has only requested consideration of the 75 IU dose in this NDA. Other doses (25, 150, 225 IU) were included in preliminary studies but only the 75 IU dose was included in the single Phase 3 study (21008).

The sponsor considers both 21008 and 6253 to be primary studies. These are the two studies which show statistically significant differences for Luveris 75 IU versus placebo. However, only 21008 was planned as a Phase 3 study. Study 6253 was designed as a Phase 2 dose-finding study. The sponsor calls the second Phase 2, dose-finding study (6905) supportive evidence. This was the Phase 2 study conducted in the U.S. When the two Phase 2 protocols were proposed to the FDA the sponsor planned them to be identical protocols. However, when the studies were conducted, the protocols were changed resulting in different patient populations. In study 6905, the entry criteria allowed enrollment of patients with baseline LH levels higher than 1.2 IU/L. A subgroup analysis of patients with low baseline LH levels from study 6905 has sample sizes too small (3 per group) to make statistical conclusions.

In the Integrated Summary of Efficacy (ISE) the sponsor summarized the data from the five clinical studies in three different ways. The "Primary Integrated Analysis" combined all the patients treated with placebo or Luveris 75 IU in studies 21008 and 6253. All these patients had low LH (< 1.2 IU/L) at baseline. The "Secondary Integrated Analysis" added patients with low baseline LH levels from studies 6905 (n=3 placebo/3 Luveris 75 IU) and 7798 (5 Luveris 75 IU). The "Tertiary Integrated Analysis" included all patients treated in the placebo or Luveris 75 IU treatment groups in the 5 studies, regardless of baseline LH. These integrated analyses did not include patients enrolled in the 25, 150, or 225 IU groups from any of the studies.

In all of the sponsor's analyses, the primary efficacy endpoint was follicular development, with patients who stopped treatment due to risk of OHSS being classified as a treatment success. Using this definition, all of the integrated efficacy analyses conclude a statistically significant difference of Luveris 75 IU versus placebo. Separate analyses by study show a statistically significant difference between the two groups in study 21008 and a statistically significant dose-related trend in study 6253 but not in study 6905.

The main issue regarding the efficacy decision is the appropriate classification of patients who stopped treatment, and therefore stopped the ovulation cycle, due to the risk of OHSS. The primary endpoint is follicular development, which is based on three variables: follicle size, pre-ovulatory E_2 level, and mid-luteal P_4 level. The protocol for study 21008 specified that "should any patient be cancelled for risk of OHSS, that patient will be counted as achieving follicular development." The sponsor gives the rationale that if the patient cancelled the ovulation cycle, she would not have the P_4 measurement needed for the follicular development criteria. In other words, canceling the ovulation cycle would result in the patient having missing data for the follicular development endpoint, so the missing data would be replaced with classification as a treatment success. The protocols for the four earlier studies are not as clear regarding this issue. The protocols for the Phase 2 studies (6253 and 6905) list the three criteria for follicular development and the planned trend test, followed by a statement that "should any patient cycle be canceled for risk of OHSS the trend test will be repeated counting overstimulation as a response." The protocols for the other two supportive studies (7798 and 8297) do not mention OHSS with respect to classification for the follicular development efficacy endpoint.

If patients who stopped treatment due to a risk of OHSS are classified as treatment success for follicular development, then two of the three placebo-controlled clinical trials (21008 and 6253) conclude Luveris 75 IU is statistically significantly different from placebo while the third study (6905) does not support this conclusion. However, if patients who stopped treatment due to a risk of OHSS are classified as treatment failures for follicular development, then none of the studies support a statistically significant difference of Luveris 75 IU versus placebo.

1.3 PRINCIPAL FINDINGS

The main focus of this review is the single Phase III study (21008). The sponsor used a Fisher's Exact test to compare the Luveris 75 IU group to the placebo group and concluded that they were significantly different (p-value = 0.023). The sponsor classified patients who discontinued treatment due to a risk of OHSS as treatment successes. When I reclassified the patients as treatment failures the results did not support a statistically significant difference between the groups (p-value = 0.063).

There were two Phase II dose-finding studies, 6253 and 6905. The sponsor used a trend test, with weights of (-2, 0, 1, 1) for the placebo, 25 IU, 75 IU, and 225 IU groups respectively. This weights the 75 IU and 225 IU doses equally. The trend test indicated a significant dose relationship (versus placebo) for study 6253 but not for study 6905. In order to assess the Luveris 75 IU dose on its own, I used a Fisher's Exact test to see how

strongly the Phase II study results could support the primary Phase III results. If patients at risk of OHSS were classified as treatment successes, study 6253 supported the statistically significant difference versus placebo but study 6905 did not (p-value = 0.028 and 1.000, respectively). However, if patients at risk of OHSS were classified as treatment failures then neither of the Phase II studies supported that conclusion (p-value = 0.157 and 0.670, respectively).

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

The desired indication for Luveris is ovulation induction in anovulatory women with hypogonadotropic hypogonadism (HH). This IND (44,108) was granted orphan drug status for this indication. The patient population was defined as having a baseline LH level < 1.2 IU/L, along with other characteristics. Most of the clinical studies submitted with this NDA have very small sample sizes per treatment group, making statistical conclusions and interpretations difficult.

2.2 DATA ANALYZED AND SOURCES

Table 1 provides details on the study designs of the five clinical studies discussed in this statistical review. SAS data sets and descriptions were provided by the sponsor on a CD dated April 30, 2001. Additional documentation regarding the efficacy variables was requested in January, 2002, and was received in a fax dated 1/10/02.

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Table 1: Overview of Clinical Studies

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
21008 (2/00 – 9/00)	25 (US, Canada, Israel, Australia)	30 Luveris 75IU n=20 Placebo n=10	Placebo	Randomized, Placebo-control, Double-blind, Multicenter, Parallel arm	1 cycle
6253 (9/93 – 4/95)	10 (Europe, Israel)	38 Luveris 25IU n=8 Luveris 75IU n=11 Luveris 225IU n=10 Placebo n=9	Placebo	Randomized, Placebo-control, Open-label, Multicenter, Parallel arm	1 to 3 cycles; Only randomized to first cycle; First cycle is primary for efficacy
6905 (7/94 – 7/97)	14 (US)	40 Luveris 25IU n=9 Luveris 75IU n=11 Luveris 225IU n=9 Placebo n=11	Placebo	Randomized, Placebo-control, Open-label, Multicenter, Parallel arm	1 to 3 cycles; Only randomized to first cycle; First cycle is primary for efficacy
7798 (9/95 – 5/98)	7 (Germany)	15 (First cycle dose:) Luveris 25IU n=5 Luveris 75IU n=5 Luveris 225IU n=5	Dose-ranging; 3 dose levels of Luveris	Randomized, Dose-ranging, Open-label, Multicenter, Crossover	1 to 3 cycles Randomized to a sequence of 3 doses; First cycle is primary for efficacy
8297 (3/96 – 8/98)	14 (Spain)	Luveris 75IU n=38	none	Open-label, Single-arm, Multicenter	1 to 3 cycles; First cycle is primary for efficacy

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

The primary focus of this statistical review is on the single Phase III placebo-controlled study (21008). Additional comparisons to placebo are possible from the two Phase II studies (6253 and 6905). Studies 7798 and 8297 provide descriptive results only.

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

In the Integrated Summary of Efficacy (ISE) the sponsor summarized the data from the five clinical studies in three different ways. The "Primary Integrated Analysis" combined all the patients treated with placebo or Luveris 75 IU in studies 21008 and 6253. All these patients had low LH (< 1.2 IU/L) at baseline. The "Secondary Integrated Analysis" added patients with low baseline LH levels from studies 6905 (n=3 placebo/3 Luveris 75 IU) and 7798 (5 Luveris 75 IU). The "Tertiary Integrated Analysis" included all patients treated in the placebo or Luveris 75 IU treatment groups in the 5 studies, regardless of baseline LH. These integrated analyses did not include patients enrolled in the 25, 150, or 225 IU groups from any of the studies.

In all of the sponsor's analyses, the primary efficacy endpoint was follicular development, with patients who stopped treatment due to risk of OHSS being classified as a treatment success. Using this definition, all of the integrated efficacy analyses conclude a statistically significant difference of Luveris 75 IU versus placebo. For each analysis, a Cochran-Mantel-Haenszel test, adjusting for study, was used.

The Primary Integrated Analysis, which combined studies 21008 and 6253, had a p-value=0.0002. The Secondary Integrated Analysis added a total of 11 patients with low baseline LH levels from studies 6905 and 7798. Lastly, the Tertiary Integrated Analysis, which included all patients treated in the placebo or Luveris 75 IU treatment groups in the 5 studies, regardless of baseline LH, had a p-value of 0.0006. Separate analyses by study show a statistically significant difference between the two groups in study 21008 and a statistically significant dose-related trend in study 6253 but not in study 6905.

2.3.2 STATISTICAL METHODOLOGIES

The ISE contained three analyses which combined patients across studies, and only included patients in the Luveris 75 IU or placebo treatment groups. The sponsor used a Cochran-Mantel-Haenszel test, adjusting for study, to compare the two treatment groups.

Study 21008 was a two-arm, placebo-controlled study. The primary endpoint is Follicular Development, a Yes/No outcome based on three criteria, all of which must be met. This study planned to use a Fisher's Exact test to compare the two groups. This is appropriate.

The two dose-finding studies (6253 and 6905) included three Luveris dose groups: 25, 75 or 225 IU, and a placebo dose group. The protocols planned for a trend test (Armitage or exact permutation) to detect a relationship between dose and follicular development. The protocols did not prespecify what weights would be applied to the dose levels. The sponsor

presents results for weights of (-2, 0, 1, 1). This model combines the 75 and 225 IU groups as being the same, and compares that group to placebo, ignoring the 25 IU group. This weighting is questionable with regard to supporting efficacy of the 75 IU dose alone. Since the sponsor is only requesting approval of the 75 IU dose, I wanted to compare that dose group alone to placebo to investigate the strength of the evidence from these studies toward supporting the 75 IU dose. Therefore I performed Fisher's Exact tests comparing the 75 IU group to the placebo group.

Each study included up to 6 secondary variables which were of interest to the Medical Officer. All were binary outcomes with patients defined as success or failure for each criterion. In general these variables are important for evaluating ovulation induction but individually do not constitute sufficient evidence. For these variables I provided p-values from a Fisher's Exact test solely for the purpose of assessing the strength of the supportive evidence. The p-values for the secondary variables are not intended to support statistical conclusions.

There were no appropriate comparisons possible from studies 7798 and 8297. The data from these studies were combined by the sponsor in the ISE to provide additional evidence.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

2.3.3.1 Study 21008

Study 21008 is a randomized, double-blind, placebo-controlled, parallel-arm study. It was conducted in 25 centers in the U.S., Canada, Israel and Australia. Subjects were randomized on a 2:1 basis to Luveris 75 IU or placebo and received treatment for 1 cycle. The primary objective was ovulation induction, with pregnancy as a secondary outcome. Patients were women, ages 18-39, with HH who desired pregnancy. Entry criteria included baseline FSH < 5 IU/L and LH < 1.2 IU/L.

The sponsor used the evaluable patient population for the efficacy analyses. This excluded patients who were major protocol violations (n=4) or who were not eligible for assessment of the primary efficacy variable (n=1). The sponsor's results are shown in Table 2.

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Table 2: Applicant's Results - Evaluable Patients (Study #21008)

	Placebo (n=10)	75 IU r-hLH (n=24)
Primary Efficacy Variable:		
Follicular Development		
Success (%)	2 (20%)	16 (67%)
Failure (%)	8 (80%)	8 (33%)
p-value=0.023 (Fisher's Exact Test)		
Secondary Efficacy Variables:		
Follicle Size:		
At Least One Follicle ≥ 17 mm		
Success (%)	4 (40%)	15 (63%)
Failure (%)	6 (60%)	9 (38%)
Pre-Ovulatory E_2 Level ≥ 109 pg/mL		
Success (%)	2 (20%)	16 (67%)
Failure (%)	8 (80%)	8 (33%)
Mid-Luteal P_4 Level ≥ 7.9 ng/mL		
Success (%)	2 (20%)	12 (50%)
Failure (%)	8 (80%)	12 (50%)
Chemical Pregnancy		
Success (%)	1 (10%)	2 (8%)
Failure (%)	9 (90%)	22 (92%)
Clinical Pregnancy		
Success (%)	1 (10%)	1 (4%)
Failure (%)	9 (90%)	23 (96%)
Risk of OHSS		
Yes (%)	1 (10%)	5 (21%)
No (%)	9 (90%)	19 (79%)

Source: Vol. 1.75: Tables 13-16, 22-23, 25.

My analysis differed from the sponsor's in two key factors. First, I used the intent-to-treat (ITT) population of all patients treated (n=39). Secondly, the Medical Officer requested that patients who stopped treatment due to Ovarian Hyperstimulation Syndrome (OHSS) be reclassified as treatment failures. A total of 7 subjects stopped treatment for this reason. Table 3 lists the subjects who were reclassified for my analyses.

Table 3: Patients Reclassified as Treatment Failures (Study #21008)

Treatment Group	Subject ID # (Reason)
Placebo	2530003 (OHSS risk)
75 IU r-hLH	2510001 (E_2 value = 106 pg/mL) 0940001 (OHSS risk) 2520002 (OHSS risk) 2530002 (OHSS risk) 2580003 (OHSS risk) 3920002 (OHSS risk) 4320003 (OHSS risk)

Source: SAS datasets

The results of my analyses are shown in Table 4. The main consideration is the between-group comparison is for the primary endpoint of follicular development. The p-values for the secondary variables are presented for the purpose of assessing the strength of the supportive evidence but are not intended to support statistical conclusions.

In the protocol, the definition of the primary efficacy variable specified that a patient who developed OHSS would be considered as achieving follicular development, a success. Using this definition and the ITT population, a Fisher's Exact test concludes that the Luveris 75 IU treatment group is statistically significantly different from the placebo group (p-value =0.008).

When the patients who developed OHSS were reclassified as treatment failures, the Fisher's Exact test gives a p-value of 0.063, indicating that there is not sufficient evidence to show Luveris 75 IU treatment group is statistically significantly different than the placebo group.

Table 4: Reviewer's Results – ITT Patients (Study #21008)

	Placebo (n=13)	75 IU r-hLH (n=26)
Primary Efficacy Variable: Protocol Definition: OHSS=success		
Follicular Development		
Success (%)	2 (15%)	16 (65%)
Failure (%)	11 (85%)	10 (35%)
p-value=0.008 (Fisher's Exact Test)		
Primary Efficacy Variable: Reclassify OHSS=failure		
Follicular Development		
Success (%)	1 (8%)	10 (38%)
Failure (%)	12 (92%)	16 (62%)
p-value=0.063 (Fisher's Exact Test)		
Secondary Efficacy Variables:		
Follicle Size:		
At Least One Follicle ≥ 17 mm		
Success (%)	4 (31%)	16 (62%)
Failure (%)	9 (69%)	10 (38%)
p-value=0.096 (Fisher's Exact Test)		
Pre-Ovulatory E_2 Level ≥ 109 pg/mL		
Success (%)	2 (15%)	16 (62%)
Failure (%)	11 (85%)	10 (38%)
p-value=0.008 (Fisher's Exact Test)		
Mid-Luteal P_4 Level ≥ 7.9 ng/mL		
Success (%)	2 (15%)	12 (46%)
Failure (%)	11 (85%)	14 (54%)
p-value=0.083 (Fisher's Exact Test)		
Chemical Pregnancy		
Success (%)	1 (8%)	2 (8%)
Failure (%)	12 (92%)	24 (92%)
p-value=1.000 (Fisher's Exact Test)		
Clinical Pregnancy		
Success (%)	1 (8%)	1 (4%)
Failure (%)	12 (92%)	25 (96%)
p-value=1.000 (Fisher's Exact Test)		
Risk of OHSS		
Yes (%)	1 (8%)	6 (23%)
No (%)	12 (92%)	20 (77%)
p-value=0.388 (Fisher's Exact Test)		

Source: SAS datasets

2.3.3.2 Study 6253

Study 6253 is a randomized, open-label, dose-finding, placebo-controlled parallel-arm study. It was conducted in 10 centers in 4 countries in Europe. Subjects were randomized on a 1:1:1:1 basis to Luveris 25, 75, or 225 IU or placebo, and received treatment for up to 3 cycles. Only the results for the first cycle will be considered for efficacy evaluation. The primary objective was to determine the minimum effective dose for ovulation induction, with pregnancy as a secondary outcome. Patients were women, ages 18-35, with HH. Volunteers did not necessarily desire pregnancy. Entry criteria included baseline FSH < 5 IU/L and LH < 1.2 IU/L.

The sponsor's analyses used the ITT patient population of all patients randomized who received at least on dose of treatment. The sponsor performed a Cochran-Armitage trend test using all four dose groups. A trend test is appropriate for a dose-finding study, but in the analysis presented by the sponsor weights of (-2, 0, 1, 1) were applied. This gives no weight to the 25 IU group, and equal weight to the 75 and 225 IU groups. A between-group test of the Luveris 75 IU group versus placebo was not planned.

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Table 5: Applicant's Results - ITT Patients (Study #6253)

	Placebo (n=9)	25 IU r-hLH (n=8)	75 IU r-hLH (n=11)	225 IU r-hLH (n=10)
Primary Efficacy Variable:				
Follicular Development				
Success (%)	1 (11%)	2 (25%)	7 (64%)	7 (70%)
Failure (%)	8 (89%)	6 (75%)	4 (36%)	3 (30%)
p-value = 0.004 (Trend test)				
Secondary Efficacy Variables:				
Follicle Size:				
At Least One Follicle ≥ 17 mm				
Success (%)	2 (22%)	4 (50%)	7 (64%)	4 (40%)
Failure (%)	7 (78%)	4 (50%)	4 (36%)	6 (60%)
Pre-Ovulatory E_2 Level ≥ 109 pg/mL				
Success (%)	1 (11%)	2 (25%)	6 (55%)	5 (50%)
Failure (%)	8 (89%)	6 (75%)	5 (45%)	5 (50%)
Mid-Luteal P_4 Level ≥ 7.9 ng/mL				
Success (%)	1 (11%)	2 (25%)	5 (45%)	5 (50%)
Failure (%)	8 (89%)	6 (75%)	6 (55%)	5 (50%)
Chemical Pregnancy				
N (patients who desired pregnancy)	7	6	9	6
Success (%)	1 (14%)	0 (0%)	2 (22%)	0 (0%)
Failure (%)	6 (86%)	6 (100%)	7 (78%)	6 (100%)
Clinical Pregnancy				
N (patients who desired pregnancy)	7	6	9	6
Success (%)	0 (0%)	0 (0%)	2 (22%)	0 (0%)
Failure (%)	7 (100%)	6 (100%)	7 (78%)	6 (100%)
Risk of OHSS				
Yes (%)	0 (0%)	0 (0%)	2 (18%)	3 (30%)
No (%)	9 (100%)	8 (100%)	9 (82%)	7 (70%)

Source: Vol. 77: Tables 23-26, 37-38

The Medical Officer requested that the results be analyzed with OHSS classified as a treatment failure. Table 6 shows the five patients who developed OHSS during the treatment.

Table 6: Patients Reclassified as Treatment Failures (Study #6253)

Treatment Group	Subject ID # (Reason)
Placebo	None
25 IU r-hLH	None
75 IU r-hLH	62530102 (OHSS risk) 62530903 (OHSS risk)
225 IU r-hLH	62530101 (OHSS risk) 62530502 (OHSS risk) 62530605 (OHSS risk)

Source: Vol. 77: Table 23

This study is considered as supportive evidence. It was planned as a dose-finding study, and the planned analysis was a trend test. Based on information from this and other studies, the sponsor selected the 75 IU dose for the confirmatory trial (#21008).

Although pairwise between-group comparisons were not planned in the protocol, I used a Fisher's Exact test to compare the Luveris 75 IU group to the placebo group to indicate how strongly these results supported the efficacy of the 75 IU dose. The results suggest that, when OHSS risk is considered as a treatment success, Luveris 75 IU is statistically different from placebo. When OHSS risk is considered as a treatment failure, there is not sufficient evidence to support a statistically significant difference vs. placebo. The reported p-values are not designed to provide a conclusive decision, only supportive evidence.

The primary endpoint is follicular development. The p-values for the secondary variables are presented for the purpose of assessing the strength of the supportive evidence but are not intended to support statistical conclusions.

Table 7: Reviewer's Results – ITT Patients (Study #6253)

	Placebo (n=9)	25 IU r-hLH (n=8)	75 IU r-hLH (n=11)	225 IU r-hLH (n=10)
Primary Efficacy Variable: Protocol Definition: OHSS=success				
Follicular Development				
Success (%)	1 (11%)	2 (25%)	7 (64%)	7 (70%)
Failure (%)	8 (89%)	6 (75%)	4 (36%)	3 (30%)
p-value vs. placebo (Fisher's Exact Test)			0.028	
Primary Efficacy Variable: Reclassify OHSS=failure				
Follicular Development				
Success (%)	1 (11%)	2 (25%)	5 (45%)	4 (40%)
Failure (%)	8 (89%)	6 (75%)	6 (55%)	6 (60%)
p-value vs. placebo (Fisher's Exact Test)			0.157	
Secondary Efficacy Variables:				
Follicle Size:				
At Least One Follicle ≥ 17 mm				
Success (%)	2 (22%)	4 (50%)	6 (55%)	4 (40%)
Failure (%)	7 (78%)	4 (50%)	5 (45%)	6 (60%)
p-value vs. placebo (Fisher's Exact Test)			0.197	
Pre-Ovulatory E_2 Level ≥ 109 pg/mL				
Success (%)	1 (11%)	2 (25%)	6 (55%)	5 (50%)
Failure (%)	8 (89%)	6 (75%)	5 (45%)	5 (50%)
p-value vs. placebo (Fisher's Exact Test)			0.070	
Mid-Luteal P_4 Level ≥ 7.9 ng/mL				
Success (%)	1 (11%)	2 (25%)	5 (45%)	5 (50%)
Failure (%)	8 (89%)	6 (75%)	6 (55%)	5 (50%)
p-value vs. placebo (Fisher's Exact Test)			0.157	
Chemical Pregnancy				
N (patients who desired pregnancy)	7	6	9	6
Success (%)	1 (14%)	0 (0%)	2 (22%)	0 (0%)
Failure (%)	6 (86%)	6 (100%)	7 (78%)	6 (100%)
p-value vs. placebo (Fisher's Exact Test)			1.000	
Clinical Pregnancy				
N (patients who desired pregnancy)	7	6	9	6
Success (%)	0 (0%)	0 (0%)	2 (22%)	0 (0%)
Failure (%)	7 (100%)	6 (100%)	7 (78%)	6 (100%)
p-value vs. placebo (Fisher's Exact Test)			0.475	
Risk of OHSS				
Yes (%)	0 (0%)	0 (0%)	2 (18%)	3 (30%)
No (%)	9 (100%)	8 (100%)	9 (82%)	7 (70%)
p-value vs. placebo (Fisher's Exact Test)			0.479	

Source: SAS datasets

All but one of the 38 subjects in Study 6253 had a baseline LH value < 1.2 IU. The single exception (patient 0801) had a baseline LH value of 1.3 IU and was assigned to the 25 IU treatment group during cycle 1. She was not a success for follicular development and did not have a risk of OHSS.

2.3.3.3 Study 6905

Study 6905 is a randomized, open-label, dose-finding, placebo-controlled parallel-arm study. It was conducted in 14 centers in the United States. Subjects were randomized on a 1:1:1:1 basis to Luveris 25, 75, or 225 IU or placebo, and received treatment for up to 3 cycles. Only the results for the first cycle will be considered for efficacy evaluation. The primary objective was to determine the minimum effective dose for ovulation induction, with pregnancy as a secondary outcome. Patients were women, ages 18-40. Volunteers did not necessarily desire pregnancy. Entry criteria included baseline FSH < 10.85 IU/L and LH < 13.3 IU/L. The title of the protocol describes the patients as anovulatory women with HH, but these entry criteria do not match the HH patient population defined for orphan drug status.

The sponsor used the All Treated patient population for the efficacy analyses. This included all patients randomized who received at least on treatment dose (n=40). Three patients were randomized but not treated.

The sponsor used a Cochran-Armitage Trend test to compare the 75 IU and 225 IU dose groups combined versus the placebo group (weights –2, 0, 1, 1). This trend test did not give any weight to the 25 IU dose group. Since the 75 IU and 225 IU dose groups were combined for the test, the results do not adequately represent the 75 IU dose for which the sponsor is requested consideration in the NDA.

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Table 8: Applicant's Results – All Treated (Study #6905)

	Placebo (n=11)	25 IU r-hLH (n=9)	75 IU r-hLH (n=11)	225 IU r-hLH (n=9)
Primary Efficacy Variable:				
Follicular Development				
Success (%)	7 (64%)	9 (100%)	8 (73%)	6 (67%)
Failure (%)	4 (36%)	0 (0%)	3 (27%)	3 (33%)
p-value = 0.774 (Trend test)				
Secondary Efficacy Variables:				
Follicle Size:				
At Least One Follicle ≥ 17 mm				
Success (%)	10 (91%)	9 (100%)	11 (100%)	7 (78%)
Failure (%)	1 (9%)	0 (0%)	0 (0%)	2 (22%)
Pre-Ovulatory E_2 Level ≥ 160 pg/mL				
Success (%)	7 (64%)	9 (100%)	9 (82%)	6 (67%)
Failure (%)	4 (36%)	0 (0%)	2 (18%)	3 (33%)
Mid-Luteal P_4 Level ≥ 10 ng/mL				
Success (%)	10 (91%)	9 (100%)	9 (82%)	7 (78%)
Failure (%)	1 (9%)	0 (0%)	2 (18%)	2 (22%)
Chemical Pregnancy				
N (patients who desired pregnancy)	10	8	10	6
Success (%)	2 (20%)	2 (25%)	3 (30%)	2 (33%)
Failure (%)	8 (80%)	6 (75%)	7 (70%)	4 (67%)
Clinical Pregnancy				
N (patients who desired pregnancy)	10	8	10	6
Success (%)	2 (20%)	1 (13%)	3 (30%)	2 (33%)
Failure (%)	8 (80%)	7 (88%)	7 (70%)	4 (67%)
Risk of OHSS				
Yes (%)	2 (18%)	2 (22%)	1 (9%)	0 (0%)
No (%)	9 (82%)	7 (78%)	10 (91%)	9 (100%)

Source: Vol. 80: Tables 13-16, 24, 36-37

The Medical Officer requested that the results be analyzed with OHSS classified as a treatment failure. Table 9 shows the five patients who developed OHSS during the treatment.

Table 9: Patients Reclassified as Treatment Failures (Study #6905)

Treatment Group	Subject ID # (Reason)
Placebo	060004 (OHSS risk) 160002 (OHSS risk)
25 IU r-hLH	010001 (OHSS risk) 030001 (OHSS risk)
75 IU r-hLH	070002 (OHSS risk)
255 IU r-hLH	None

Source: SAS datasets

The efficacy criteria for this study were somewhat different from the Phase III study. Specifically, the E_2 criterion used a cutoff of ≥ 160 pg/mL rather than ≥ 109 pg/mL, and the P_4 criterion used a cutoff of ≥10.0 ng/mL rather than ≥7.9 ng/mL. One patient in the 225 IU treatment group did not meet the E_2 criterion of 160 but would have met the 109 criterion. There were no differences for the P_4 criterion.

The primary endpoint is follicular development. The sponsor did not plan for a pairwise comparison of the 75IU group to the placebo group because this study was intended for dose-finding. I used a Fisher's Exact test for that comparison to indicate how strongly this study supported the efficacy of the 75 IU dose. The results suggest there is insufficient evidence to conclude a statistically significant difference between Luveris 75 IU and placebo. The p-values for the secondary variables are presented for the purpose of assessing the strength of the supportive evidence but are not intended to support statistical conclusions.

Table 10: Reviewer's Results ITT Patients (Study #6905)

	Placebo (n=11)	25 IU r-hLH (n=9)	75 IU r-hLH (n=11)	225 IU r-hLH (n=9)
Primary Efficacy Variable: Protocol Definition: OHSS=success				
Follicular Development				
Success (%)	7 (64%)	9 (100%)	8 (73%)	6 (67%)
Failure (%)	4 (36%)	0 (0%)	3 (27%)	3 (33%)
p-value vs. placebo (Fisher's Exact Test)			1.000	
Primary Efficacy Variable: Reclassify OHSS=failure				
Follicular Development				
Success (%)	5 (45%)	7 (78%)	7 (64%)	6 (67%)
Failure (%)	6 (55%)	2 (22%)	4 (36%)	3 (33%)
p-value vs. placebo (Fisher's Exact Test)			0.670	
Secondary Efficacy Variables:				
Follicle Size:				
At Least One Follicle ≥ 17 mm				
Success (%)	8 (73%)	7 (78%)	10 (91%)	7 (78%)
Failure (%)	3 (27%)	2 (22%)	1 (9%)	2 (22%)
p-value vs. placebo (Fisher's Exact Test)			0.587	
Pre-Ovulatory E_2 Level ≥ 160 pg/mL				
Success (%)	5 (45%)	7 (78%)	8 (73%)	6 (67%)
Failure (%)	6 (55%)	2 (22%)	3 (27%)	3 (33%)
p-value vs. placebo (Fisher's Exact Test)			0.387	
Mid-Luteal P_4 Level ≥ 10.0 ng/mL				
Success (%)	8 (73%)	7 (78%)	8 (73%)	7 (78%)
Failure (%)	3 (27%)	2 (22%)	3 (27%)	2 (22%)
p-value vs. placebo (Fisher's Exact Test)			1.000	
Chemical Pregnancy				
N (patients who desired pregnancy)	10	8	10	6
Success (%)	2 (20%)	2 (25%)	3 (30%)	2 (33%)
Failure (%)	8 (80%)	6 (75%)	7 (70%)	4 (67%)
p-value vs. placebo (Fisher's Exact Test)			1.000	
Clinical Pregnancy				
N (patients who desired pregnancy)	10	8	10	6
Success (%)	2 (20%)	1 (13%)	3 (30%)	2 (33%)
Failure (%)	8 (80%)	7 (88%)	7 (70%)	4 (67%)
p-value vs. placebo (Fisher's Exact Test)			1.000	
Risk of OHSS				
Yes (%)	2 (18%)	2 (22%)	1 (9%)	0 (0%)
No (%)	9 (82%)	7 (78%)	10 (91%)	9 (100%)
p-value vs. placebo (Fisher's Exact Test)			1.000	

Source: SAS datasets

The inclusion criteria for this study allowed enrollment of women with baseline LH levels up to 13.3 IU/L. This was a different patient population than the phase III study (21008). Therefore I looked at subgroups of patients based on the baseline LH levels. The Medical Officer requested the categories defined in Table 11.

Table 11: Baseline LH Level by Treatment Group (Study #6905)

Baseline LH Category	Placebo (n=11)	25 IU r-hLH (n=9)	75 IU r-hLH (n=11)	225 IU r-hLH (n=9)	Total (n=40)
< 1.2 IU	3 (27%)	5 (56%)	3 (27%)	4 (44%)	15 (38%)
1.2 – 5.0 IU	7 (64%)	4 (44%)	5 (45%)	3 (33%)	19 (48%)
> 5.0 IU	1 (9%)	0 (0%)	3 (27%)	2 (22%)	6 (15%)

Source: Vol. 83 pg. 97-98.

Table 12 shows the results of four endpoints of particular interest for the Medical Officer for the Luveris 75 IU treatment group (desired dose) by baseline LH category. Table 13 presents the same endpoints for the Low LH (<1.2 IU) subgroup (intended patient population) by treatment group.

Table 12: Subgroup Analyses by Baseline LH Level: 75 IU Treatment Group (Study #6905)

Subgroup: Patients Randomized to 75 IU Treatment Group	Base LH < 1.2 IU n=3	Base LH 1.2 – 5.0 IU n=5	Base LH > 5.0 IU n=3
Primary Efficacy Variable: Protocol Definition: OHSS=success			
Follicular Development			
Success (%)	2 (67%)	3 (60%)	3 (100%)
Failure (%)	1 (33%)	2 (40%)	0 (0%)
Primary Efficacy Variable: Reclassify OHSS=failure			
Follicular Development			
Success (%)	2 (67%)	3 (60%)	2 (67%)
Failure (%)	1 (33%)	2 (40%)	1 (33%)
Clinical Pregnancy			
Success (%)	1 (33%)	2 (40%)	0 (0%)
Failure (%)	2 (67%)	3 (60%)	3 (100%)
Risk of OHSS			
Yes (%)	0 (0%)	0 (0%)	1 (33%)
No (%)	3 (100%)	5 (100%)	2 (67%)

Source: SAS datasets

Table 13: Efficacy Results – ITT Patients: Low LH (<1.2 IU) Subgroup (Study #6905)

	Placebo (n=3)	25 IU r-hLH (n=5)	75 IU r-hLH (n=3)	225 IU r-hLH (n=4)
Primary Efficacy Variable: Protocol Definition: OHSS=success				
Follicular Development				
Success (%)	0 (0%)	5 (100%)	2 (67%)	3 (75%)
Failure (%)	3 (100%)	0 (0%)	1 (33%)	1 (25%)
Primary Efficacy Variable: Reclassify OHSS=failure				
Follicular Development				
Success (%)	0 (0%)	4 (80%)	2 (67%)	3 (75%)
Failure (%)	3 (100%)	1 (20%)	1 (33%)	1 (25%)
Risk of OHSS				
Yes (%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)
No (%)	3 (100%)	4 (80%)	3 (100%)	4 (100%)

Source: SAS datasets

2.3.3.4 Study 7798

Study 7798 is a randomized, open-label, dose-finding, crossover study. It was conducted in 7 centers in Germany. Subjects were randomized equally to a treatment sequence which consisted of Luveris 75, 150, and 225 IU in a prespecified order over 3 cycles. Each subject received a consistent dose during each cycle, then switched dose for the next cycle. Only the results for the first cycle will be considered for efficacy evaluation. The primary objective was to determine the efficacy of Luveris for ovulation induction, with pregnancy as a secondary outcome. Patients were women, ages 18-39, with HH, who desired pregnancy. Entry criteria included baseline FSH < 5 IU/L and LH < 1.2 IU/L. This is a small, exploratory study, and no statistical conclusions can be tested from this study.

In the study report, the sponsor did not classify patients with OHSS risk as treatment success. Only subjects who met the criteria for follicular development, including the P_4 measurement, were counted as successes. The two subjects who discontinued due to risk of OHSS did not have a P_4 measurement. The sponsor's results are shown in Table 14.

Table 14: Applicant's Results ITT Patients (Study #7798)

	75 IU r-hLH (n=5)	150 IU r-hLH (n=5)	225 IU r-hLH (n=5)
Primary Efficacy Variable:			
Follicular Development			
Success (%)	2 (40%)	1 (20%)	3 (60%)
Failure (%)	3 (60%)	4 (80%)	2 (40%)
Secondary Efficacy Variables:			
Follicle Size:			
At Least One Follicle ≥ 17 mm			
Success (%)	4 (80%)	4 (80%)	5 (100%)
Failure (%)	1 (20%)	1 (20%)	0 (0%)
Pre-Ovulatory E_2 Level ≥ 200 pg/mL			
Success (%)	3 (60%)	2 (40%)	5 (100%)
Failure (%)	2 (40%)	3 (60%)	0 (0%)
Mid-Luteal P_4 Level ≥ 10 ng/mL			
Success (%)	3 (60%)	3 (60%)	3 (60%)
Failure (%)	2 (40%)	2 (40%)	2 (40%)
Chemical Pregnancy	Not reported		
Success (%)			
Failure (%)			
Clinical Pregnancy			
Success (%)	1 (20%)	0 (0%)	0 (0%)
Failure (%)	4 (80%)	5 (100%)	5 (100%)
Risk of OHSS			
Yes (%)	1 (20%)	0 (0%)	1 (20%)
No (%)	4 (80%)	5 (100%)	4 (80%)

Source: Vol. 85: Tables 13-16, 18, 27

Table 15 lists the two patients who discontinued the treatment cycle due to the risk of OHSS.

Table 15: Patients with OHSS risk (Study #7798)

Treatment Group	Subject ID # (Reason)
75 IU r-hLH	Center 09 Patient 11 (OHSS risk)
150 IU r-hLH	None
255 IU r-hLH	Center 01 Patient 13 (OHSS risk)

Source: SAS datasets

The efficacy criteria for this study were somewhat different from the Phase III study. Specifically, the E_2 criterion used a cutoff of ≥ 200 pg/mL rather than ≥ 109 pg/mL, and the P_4 criterion used a cutoff of ≥10.0 ng/mL rather than ≥7.9 ng/mL. Three patients (1 in 75 IU group; 2 in 150 IU group) did not meet the E_2 criterion of 200 but would have met the criterion of 109. There were no differences for the P_4 criterion.

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Table 16: Reviewer's Results ITT Patients (Study #7798)

	75 IU r-hLH (n=5)	150 IU r-hLH (n=5)	225 IU r-hLH (n=5)
Primary Efficacy Variable: (OHSS=failure)			
Follicular Development			
Success (%)	1 (20%)	0 (0%)	2 (40%)
Failure (%)	4 (80%)	5 (100%)	3 (60%)
Secondary Efficacy Variables:			
Follicle Size:			
At Least One Follicle ≥ 17 mm			
Success (%)	2 (40%)	2 (40%)	3 (60%)
Failure (%)	3 (60%)	3 (60%)	2 (40%)
Pre-Ovulatory E_2 Level ≥ 200 pg/mL			
Success (%)	2 (40%)	2 (40%)	4 (20%)
Failure (%)	3 (60%)	3 (60%)	1 (80%)
Mid-Luteal P_4 Level ≥ 10 ng/mL			
Success (%)	3 (60%)	3 (60%)	3 (60%)
Failure (%)	2 (40%)	2 (40%)	2 (40%)
Chemical Pregnancy			
Success (%)	1 (20%)	0 (0%)	1 (20%)
Failure (%)	4 (80%)	5 (100%)	4 (80%)
Clinical Pregnancy			
Success (%)	1 (20%)	0 (0%)	0 (0%)
Failure (%)	4 (80%)	5 (100%)	5 (100%)
Risk of OHSS			
Yes (%)	1 (20%)	0 (0%)	1 (20%)
No (%)	4 (80%)	5 (100%)	4 (80%)

Source: SAS datasets

All but one of the 15 subjects had a baseline LH value < 1.2 IU. The single exception (patient 13) had a baseline LH value of 1.2 IU, was assigned to the 225 IU treatment group during cycle 1, and discontinued due to risk of OHSS.

2.3.3.5 Study 8297

Study 8297 is a randomized, open-label, dose-finding, crossover study. It was conducted in 7 centers in Germany. Subjects were randomized equally to a treatment sequence which consisted of Luveris 75, 150, and 225 IU in a pre-specified order over 3 cycles. Each subject received a consistent dose during each cycle, then switched dose for the next cycle. Only the results for the first cycle will be considered for efficacy evaluation. The primary objective was to determine the efficacy of Luveris for ovulation induction, with pregnancy as a secondary outcome. Patients were women, ages 18-35, who desired pregnancy. Entry criteria included baseline FSH and LH levels "below or within the reference range." The patient population was described as LH and FSH deficient anovulatory women (WHO group I) but these entry criteria do not match the HH patient population defined for orphan drug status.

The primary endpoint for this study was follicular development. However, the protocol definition did not specify a criterion for the E_2 value - only criteria for follicle size and P_4 value. The protocol criterion for follicle size was at least one follicle with mean diameter ≥ 18 mm and the criterion for mid-luteal P_4 was level ≥ 30 nmol/L. The protocol did not mention how subjects who discontinued due to risk of OHSS would be classified, but in the study report analysis those patients were classified as a treatment success. The sponsor's results are shown in Table 17.

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Table 17: Applicant's Results (Study #8297)

	75 IU r-hLH (n=38)
Primary Efficacy Variable: Follicular Development	
Success (%)	31 (82%)
Failure (%)	7 (18%)
Secondary Efficacy Variables:	
Follicle Size: At Least One Follicle ≥ 18 mm	
Success (%)	33 (87%)
Failure (%)	5 (13%)
Pre-Ovulatory E_2 Level	Not Reported
Success (%)	
Failure (%)	
Mid-Luteal P_4 Level ≥ 30 nmol/L	
Success (%)	22 (58%)
Failure (%)	16 (42%)
Chemical Pregnancy	Not Reported
Success (%)	
Failure (%)	
Clinical Pregnancy	
Success (%)	4 (11%)
Failure (%)	34 (89%)
Risk of OHSS	
Yes (%)	10 (26%)
No (%)	28 (74%)

Source: Vol. 86: Tables 9-13, 26

Table 18: Patients Reclassified as Treatment Failures (Study #8297)

Treatment Group	Subject ID # (Reason)
75 IU r-hLH	101, 102, 104, 105, 106, 503, 504, 901, 1101, 1602 (OHSS risk)

Source: SAS datasets

The efficacy criteria for this study were somewhat different from the Phase III study. Specifically, there was no E_2 criterion for the primary efficacy variable of follicular

development (rather than ≥ 109 pg/mL); the follicular size criterion was at least one follicle ≥ 18 mm (rather than ≥17 mm), and the P_4 criterion used a cutoff of ≥ 30.0 nmol/L rather than ≥ 7.9 ng/mL. All subjects who qualified based on the follicle size criterion of 18mm would have qualified on the 17mm criterion, and all subjects who qualified based on the P_4 criterion of 30.0 nmol/L would have qualified on the 7.9 ng/mL criterion.

For my analyses, I calculated the number of subjects who would have qualified on the E_2 criterion of 109 pg/mL if it had applied to this study. This is only for descriptive purposes for the secondary endpoint to relate this study to the to the Phase III study. I am not redefining success for the primary endpoint of follicular development.

Table 19: Reviewer's Results (Study #8297)

	75 IU r-hLH (n=38)
Primary Efficacy Variable: Protocol Definition: OHSS not success	
Follicular Development	
Success (%)	21 (55%)
Failure (%)	17 (45%)
Secondary Efficacy Variables:	
Follicle Size:	
At Least One Follicle ≥ 18 mm	
Success (%)	30 (79%)
Failure (%)	8 (21%)
Pre-Ovulatory E_2 Level ≥ 109 pg/mL	
Success (%)	17 (45%)
Failure (%)	21 (55%)
Mid-Luteal P_4 Level ≥ 30 nmol/L	
Success (%)	22 (58%)
Failure (%)	16 (42%)
Chemical Pregnancy	
Success (%)	4 (11%)
Failure (%)	34 (89%)
Clinical Pregnancy	
Success (%)	4 (11%)
Failure (%)	34 (89%)
Risk of OHSS	
Yes (%)	10 (26%)
No (%)	28 (74%)

Source: SAS datasets

This study enrolled subjects with baseline LH values greater than 1.2 IU/L. Therefore I looked at subgroups of patients based on the baseline LH levels. The Medical Officer requested the categories and endpoints shown in Table 20.

Table 20: Subgroup Analyses for Baseline LH Level (Study #8297)

	Base LH < 1.2 IU n=22	Base LH 1.2 – 5.0 IU n=13	Base LH > 5.0 IU n=3
Primary Efficacy Variable: Protocol Definition: OHSS not success			
Follicular Development			
Success (%)	13 (59%)	6 (46%)	2 (67%)
Failure (%)	9 (41%)	7 (54%)	1 (33%)
Clinical Pregnancy			
Success (%)	2 (9%)	1 (8%)	1 (33%)
Failure (%)	20 (91%)	12 (92%)	2 (67%)
Risk of OHSS			
Yes (%)	4 (18%)	5 (38%)	1 (33%)
No (%)	18 (82%)	8 (62%)	2 (67%)

Source: SAS datasets

2.3.4 STATISTICAL REVIEWER'S FINDINGS

The primary efficacy decision for the Luveris 75 IU dose focuses on a single placebo-controlled study (21008). The primary efficacy endpoint is follicular development. Based on the definition of follicular development from the protocol (risk of OHSS=success), the Luveris 75 IU dose is statistically different from placebo (p-value = 0.023). However, the Medical Officer requested that the follicular development endpoint be analyzed with risk of OHSS reclassified as a treatment failure. Using that definition, the Luveris 75 IU treatment group is only marginally statistically different from placebo (p-value = 0.063). The Medical Officer will address the clinical relevance of the latter result in his review.

Two Phase 2 dose-finding studies (6253 and 6905) were submitted as supportive evidence. Both were randomized, double-blind parallel-arm studies with 25, 75, and 225 IU Luveris dose groups along with a placebo control group. The results from study 6253 were similar to Study 21008 and supported the same conclusions regarding the Luveris 75 IU dose. However, study 6905 did not suggest a statistically significant difference between the Luveris 75 IU treatment group and the placebo group.

Additional supportive evidence was provided from two other studies. Study 7798 was a small crossover study (n=5 per dose group) with no placebo control. Study 8297 was a single-arm study with 38 patients assigned to the Luveris 75 IU dose. These provide descriptive evidence only. No statistical conclusions can be drawn from these two studies.

The main issue regarding the efficacy decision is the appropriate classification of patients who stopped treatment, and therefore stopped the ovulation cycle, due to the risk of OHSS. If patients who stopped treatment due to a risk of OHSS are classified as treatment successes for follicular development, then two of the three placebo-controlled clinical trials conclude Luveris 75 IU is statistically significantly different from placebo while the third study does not support this conclusion. However, if patients who stopped treatment due to a risk of OHSS are classified as treatment failures for follicular development, none of the studies support a statistically significant difference of Luveris 75 IU versus placebo. The final decision on that issue rests with the Medical Officers.

2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses are included in the main efficacy analyses (Section 2.3) because the NDA is for an orphan patient population of women with HH (baseline LH < 1.2 IU/L). Some of the studies enrolled patients with higher baseline LH levels.

In three studies (2100, 6253, and 7798) all the patients assigned to the Luveris 75 IU dose or placebo treatment groups were low LH patients, so there was no change in those results. In study 6905 only 27% of the patients in the Luveris 75 IU dose or placebo treatment groups were low LH patients but the numbers were too small (3 per group) to make conclusions. In study 8297, 58% of patients in the Luveris 75 IU dose group had low LH. There was no comparator group in that study. The success rate for follicular development was similar in the low LH subgroup as seen with patients with higher LH in the same study.

2.5 CONCLUSIONS AND RECOMMENDATIONS

The results of the statistical analyses of the clinical trials cannot fully address the sufficiency of evidence to support efficacy. The primary issue is whether patients who discontinued the treatment cycle due to risk of Ovarian Hyperstimulation Syndrome (OHSS) should be classified as treatment successes or failures for follicular development. If they are classified as treatment successes, the single Phase 3 study and one of the two Phase 2 studies support the conclusion that Luveris 75 IU is statistically significantly different than placebo. However, if those patients are classified as treatment failures, none of the studies support that conclusion.

2.6 LABELLING COMMENTS

If a label were developed for Luveris 75 IU, my main recommendation would be that the issue regarding patients who discontinued the treatment cycle due to risk of Ovarian Hyperstimulation Syndrome (OHSS) be explained very clearly and prominently. In addition, if either of the Phase 2 studies (6253 or 6905) is included in the clinical study section then both should be. Equal balance should be presented for these two studies given that one was

successful for the product and the other failed. Lastly, the results of the ITT patient population should be presented rather than the evaluable patient population.

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Mike Welch
3/1/02 01:33:54 PM
BIOMETRICS
Concur with review

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

Statistical review of carcinogencity studies

No carcinogenicity studies were performed with this product.

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

CAC/ECAC Report

No CAC/ECAC was needed for this product.

2/07/02

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