

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-322**

**Clinical Pharmacology and Biopharmaceutics  
Review**

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>		<b>Clinical Pharmacology &amp; Biopharmaceutics (HFD 870) Tracking/Action Sheet for Formal/Informal Consults</b>	
<b>From: S.W. Johnny Lau, R.Ph., Ph.D.</b>		<b>To: DOCUMENT ROOM (LOG-IN and LOG-OUT)</b> Please log-in this consult and review action for the specified IND/NDA submission	
<b>DATE: 3/22/2001</b>	<b>IND No.: 44,108 Serial No.:</b>	<b>NDA No. 21-322</b>	<b>DATE OF DOCUMENT 2/27/2001</b>
<b>NAME OF DRUG lutropin alfa for injection (recombinant human luteinizing hormone)</b>		<b>PRIORITY CONSIDERATION N/A</b>	<b>DATE OF INFORMAL/FORMAL CONSULT 3/6/2001</b>
<b>NAME OF THE SPONSOR: Serono, Inc.</b>			
<b>TYPE OF SUBMISSION</b> <b>CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE</b>			
<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED			
<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input checked="" type="checkbox"/> MEETING PACKAGE (request for guidance)			
<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input type="checkbox"/> OTHER: General Correspondence (Request for Information)			
<b>REVIEW ACTION</b>			
<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)			
<input type="checkbox"/> Oral communication with Name: [ ] <input type="checkbox"/> Comments communicated in meeting/Telecon.			
<input checked="" type="checkbox"/> Formal Review/Memo (attached) <input type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER (SPECIFY BELOW): [ ]			
<b>REVIEW COMMENT(S)</b>			
<input checked="" type="checkbox"/> <b>NEED TO BE COMMUNICATED TO THE SPONSOR</b> <input type="checkbox"/> <b>HAVE BEEN COMMUNICATED TO THE SPONSOR</b>			
<b>COMMENTS:</b> The clinically tested formulation and the to-be-marketed formulation differ only in the addition of methionine to the to-be-marketed formulation. Bioequivalence study indicated that all luteinizing hormone C <sub>max</sub> and AUC parameters were within the regulatory bioequivalence criteria of 80 to 125%, except the luteinizing hormone AUC <sub>0-last</sub> .  Sponsor should provide the clinical argument or justification for the acceptability of 90% confidence interval of luteinizing hormone AUC <sub>0-last</sub> being between [     ], even though the regulatory 90% confidence interval for bioequivalence criteria is between 80 and 125%. Sponsor should document that the old and new formulation are equally safe and effective via scientific arguments.			
<b>SIGNATURE OF REVIEWER:</b> _____		Date _____	
<b>SIGNATURE OF TEAM LEADER:</b> _____		Date _____	
<b>CC.: HFD-870 DD: Malinowski TL: Parekh Rev: Lau HFD-580 PM: De-Guia</b>			Date _____

**Background:**

Sponsor develops the recombinant human luteinizing hormone (r-hLH, lyophilized lutropin alfa, Luveris™; subcutaneous injection), which was granted (October 7, 1994) an orphan drug designation (94-802) to stimulate follicular development and ovulation in infertile women with severe deficiency in LH and FSH. Sponsor intends to market the (new) formulation with 0.1 mg methionine (see Attachment). However, the pivotal and supportive clinical safety and efficacy studies were conducted with the (old) formulation without methionine. Study 22372 was conducted to assess the bioequivalence of the new versus old formulations following subcutaneous injection of 450 IU of Luveris™ in pituitary down-regulated premenopausal female volunteers (see Attachment). Results for all LH C<sub>max</sub> and AUC parameters were within the regulatory bioequivalence criteria of 80 to 125%, except that LH AUC<sub>0-last</sub> was between [       ] Hence, sponsor requested a meeting to seek guidance from HFD-580 for which formulation to submit for NDA 21-322.

A meeting will not be granted at this time and written response to sponsor's question will be sent to the sponsor instead. Study 22372 will not be reviewed at this time and will be reviewed at subsequent NDA submission. See front page for comments to the sponsor.

**Attachment starts from here.**

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4 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

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

/s/

-----  
S.W. Johnny Lau  
10/19/01 04:47:16 PM  
BIOPHARMACEUTICS

Ameeta Parekh  
10/25/01 01:14:16 PM  
BIOPHARMACEUTICS  
I concur

**Office of Clinical Pharmacology and Biopharmaceutics**  
**New Drug Application Filing and Review Form**

**General Information About the Submission**

	Information		Information
<i>NDA Number</i>	21-322	<i>Brand Name</i>	LUVERIS
<i>OCPB Division (I, II, III)</i>	DPE II (HFD 870)	<i>Generic Name</i>	Lutropin alfa for injection (r-hLH)
<i>Medical Division</i>	DRUDP (HFD 580)	<i>Drug Class</i>	Hormone (LH) replacement
<i>OCPB Reviewer</i>	Dhruba J. Chatterjee, Ph.D.	<i>Indication(s)</i>	Stimulation of follicular development and ovulation in infertile women with LH deficiencies
<i>OCPB Team Leader</i>	Ameeta Parekh, Ph.D.	<i>Dosage Form</i>	Injectable
<i>Date of Submission</i>	5/12/2001	<i>Dosing Regimen</i>	Daily for a maximum of 14 days
<i>Estimated Due Date of OCPB Review</i>	1/12/2002	<i>Route of Administration</i>	Subcutaneous
<i>PDUFA Due Date</i>	5/12/2002	<i>Sponsor</i>	Serono Inc.
<i>Division Due Date</i>	2/12/2002	<i>Priority Classification</i>	3S

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	4		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X			
multiple dose:	X			
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
body wt.				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVC):				
Bio-wavier request based on BCS				
BCS class				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	4			
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)	Is the "To-be-marketed" formulation the same as the "clinical trial formulation?" Answer : NO (see below)			
Other comments or information not included above	"To-be-marketed" formulation has methionine $\text{C}$ and this substance was not present in the clinical trial formulation. A linking bioequivalence study was conducted to prove bioequivalence of the two formulations, and the results have been submitted in this NDA.			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

**Office of Clinical Pharmacology and Biopharmaceutics  
New Drug Application Filing and Review Form**

**General Information About the Submission**

	Information		Information
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<i>Medical Division</i>	DRUDP (HFD 580)	<i>Drug Class</i>	Hormone (LH) replacement
<i>OCPB Reviewer</i>	Dhruba J. Chatterjee, Ph.D.	<i>Indication(s)</i>	Stimulation of follicular development and ovulation in infertile women with LH deficiencies
<i>OCPB Team Leader</i>	Ameeta Parekh, Ph.D.	<i>Dosage Form</i>	Injectable
<i>Date of Submission</i>	5/1/2001	<i>Dosing Regimen</i>	Daily for a maximum of 14 days
<i>Estimated Due Date of OCPB Review</i>	1/31/2002	<i>Route of Administration</i>	Subcutaneous
<i>PDUFA Due Date</i>	3/01/2002	<i>Sponsor</i>	Serono Inc.
<i>Division Due Date</i>	2/15/2002	<i>Priority Classification</i>	3S

**Clin. Pharm. and Biopharm. Information**

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Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
body wt.				
renal impairment:				

hepatic impairment:				
PD:				
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Phase 3:				
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traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>	<b>4</b>			
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
<b>QBR questions (key issues to be considered)</b>	<b>Is the "To-be-marketed" formulation the same as the "clinical trial formulation?"</b> Answer : NO (see below)			
<b>Other comments or information not included above</b>	"To-be-marketed" formulation has methionine [ ] and this substance was not present in the clinical trial formulation. A linking bioequivalence study was conducted to prove bioequivalence of the two formulations, and the results have been submitted in this NDA.			
<b>Primary reviewer Signature and Date</b>				
<b>Secondary reviewer Signature and Date</b>				

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

OCPB Briefing (2/15/02) was attended by DJ. Chatterjee, A. Parekh, J. Hunt, R. Bennett, A. Reddy & M. Kober.

## Clinical Pharmacology & Biopharmaceutics Review

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**NDA:** 21-322

**Product Trade Name:** LUVERIS™ (lutropin alfa for injection)

**Active Ingredient/s:** Recombinant Human Luteinizing Hormone (r-hLH; 75 IU)

**Indication:** Induction of Ovulation (concomitant with r-hFSH)

**Submission Dates:** 5/12/2001 (original NDA); 12/17/01

**Sponsor:** Serono, Inc.

**Submission/Priority Type:** Original/3S

**Reviewer:** Dhruba J. Chatterjee, Ph.D.

**Team Leader:** Ameeta Parekh, Ph.D.

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## **Synopsis**

The subject of this submission, LUVERIS™ (lutropin alfa for injection) is composed of recombinant human luteinizing hormone, r-hLH. Lutropin alfa for injection is a heterodimeric glycoprotein consisting of two non-covalently linked subunits (designated  $\alpha$  and  $\beta$ ) of 92 and 121 amino acids, respectively. Luveris™ is a sterile, lyophilized powder intended for co-administration with r-hFSH as a subcutaneous (sc) injection after reconstitution with Sterile Water for Injection, USP. The physicochemical, immunological, and biological activities of r-hLH are comparable to those of human pituitary and human menopausal urine-derived LH. Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. The main goal of therapy is the treatment of infertility and achievement of pregnancy.

## ***RECOMMENDATION***

From an OCPB perspective, the application is acceptable. There are no outstanding issues at this time.

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## **Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings**

- 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 parameters from the subcutaneous 75 IU dose (to be marketed product) due to the fact that the dose was low and baseline LH levels interfered in the analysis. However, PK profiles from immediate higher doses (150 and 300 IU) 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/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 formulation is acceptable and the new formulation may be marketed replacing the old (clinical trial) formulation.

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## Background

### *Questions addressed in this section:*

*What are the highlights of chemistry and formulation of the drug and drug product?*

*What is the mechanism of action, proposed indication and main goal of therapy?*

*What are other drugs available in this class, and what is its foreign marketing history?*

The subject of this submission, LUVERIS™ (lutropin alfa for injection) is composed of recombinant human luteinizing hormone, r-hLH. Lutropin alfa for injection is a heterodimeric glycoprotein consisting of two non-covalently linked subunits (designated  $\alpha$  and  $\beta$ ) of 92 and 121 amino acids, respectively. The carbohydrate chain attachment to the r-hLH protein core occurs via N- but not O-linkage. The N glycosylation sites are Asn-52 and Asn-78 for the  $\alpha$ -subunit and Asn-30 for the  $\beta$ -subunit. The primary structure of the  $\alpha$  - chain of r-hLH is identical to that of the  $\alpha$  - chain of hCG, FSH and TSH. The glycoform pattern of the  $\alpha$  - subunit of r-hLH is closely comparable to pituitary derived hLH, the differences mainly being due to the branching and sialylation extent of the oligosaccharides. The  $\beta$  - chain has an N-glycosylation site and its structure and glycosylation pattern are very similar to that of pituitary-derived hLH.

Luveris™ is a sterile, lyophilized powder intended for co-administration with r-hFSH as a subcutaneous (sc) injection after reconstitution with Sterile Water for Injection, USP. Each vial of Luveris™ contains 82.5 IU lutropin alfa, 48 mg sucrose, 0.83 mg dibasic sodium phosphate dihydrate, 0.052 mg monobasic sodium phosphate monohydrate, 0.05 mg polysorbate 20, 0.1 mg L-methionine and phosphoric acid and/or sodium hydroxide to adjust the pH. After reconstitution with one vial of enclosed diluent, the product will deliver 75 IU of recombinant human luteinizing hormone. The pH of the reconstituted solution is 7.5 to 8.5.

The physicochemical, immunological, and biological activities of r-hLH are comparable to those of human pituitary and human menopausal urine-derived LH. In the ovaries, during the follicular phase, LH stimulates theca cells to secrete androgens, which will be used as the substrate by granulosa cell aromatase enzyme to produce estradiol, supporting Follicle-Stimulating Hormone (FSH)-induced follicular development. Luveris™ is administered concomitantly with r-hFSH to stimulate development of a competent follicle and to indirectly prepare the reproductive tract for implantation and pregnancy.

Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. The main goal of therapy is the treatment of infertility and achievement of pregnancy.

Serono Inc., has recently been granted marketing authorization for the recombinant LH product in several countries including the European Union. However, as of January 2001, this product has not been marketed in any country. This is the first application seeking approval for a purified 'LH-only' product. Combination of LH and FSH is available as menotropins for injections for many years. Purified recombinant human FSH (Gonal F and Follistim) is available as an 'FSH-only' product.

## Clinical Pharmacology

### *Q. What are the single and multiple dose pharmacokinetic properties of r-hLH?*

#### Single Dose

**Study 6135** was a phase I study to assess the pharmacokinetics of recombinant-human luteinizing hormone (r-hLH) after single IV administration of increasing doses compared to a single dose of Pergonal® (hMG) in 12 healthy female volunteers down regulated with Goserelin (Zoladex®).

The primary PK objectives of this study were:

- To assess the pharmacokinetic characteristics and linearity of r-hLH following IV administration of two low (75 and 300 IU) and two high (10,000 and 40,000 IU) doses of the compound injected to 12 healthy female volunteers.
- To compare the pharmacokinetics of r-hLH with that of u-hLH contained in the hMG preparation (Pergonal® 300 IU of u-hLH and 300 IU of u-hFSH) following a single IV injection.

Blood samples were collected at the following time-points: 0 (pre-dose), 5 min, 10 min, 30 min, 1, 2, 4, 6, 9, 12, 24, 48, and 72 h, and up to 144 h for the two high doses. Urine samples were also collected during the following time intervals post-dose: 0-2h, 2-6h, 6-12h, 12-36h, and 36-60h.

#### Results:

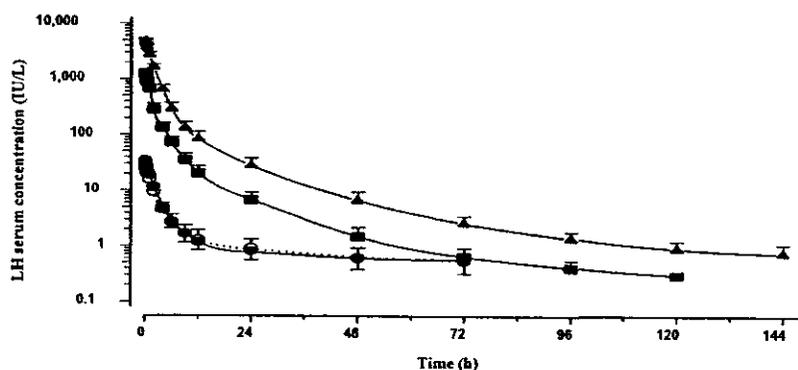
**Table 1.** Model-dependent pharmacokinetic estimates obtained after increasing IV r-hLH doses administered to healthy pre-menopausal down-regulated females (Study 6135, mean  $\pm$  SD) (n=12)

Parameters*	r-hLH <sup>†</sup>				u-hLH <sup>‡</sup>
	75	300	10,000	40,000	300
Nominal Dose (IU)	75	300	10,000	40,000	300
Immunocontent (IU)	33	132	4 560	18 240	87
AUC (IU·h/L)	13 $\pm$ 4	84 $\pm$ 14	2 625 $\pm$ 421	11 089 $\pm$ 1 711	80 $\pm$ 20
C <sub>max</sub> (IU/L)	7 $\pm$ 2	35 $\pm$ 6	1 221 $\pm$ 200	4 744 $\pm$ 535	27 $\pm$ 5
CL (L/h)	3 $\pm$ 2	1.6 $\pm$ 0.3	1.8 $\pm$ 0.3	1.7 $\pm$ 0.3	1.2 $\pm$ 0.3
CL <sub>renal</sub> (L/h)	0.12	0.03 $\pm$ 0.03	0.06 $\pm$ 0.02	0.05 $\pm$ 0.01	0.33 $\pm$ 0.22
t <sub>1/2<math>\lambda_1</math></sub> (h)	1.1 $\pm$ 0.2	1.2 $\pm$ 0.2	1.2 $\pm$ 0.2	1.3 $\pm$ 0.2	1.2 $\pm$ 0.2
t <sub>1/2</sub> (h)	NA	11 $\pm$ 8	9 $\pm$ 2	11 $\pm$ 1	12 $\pm$ 12
V <sub>ss</sub> (L)	5 $\pm$ 3	10 $\pm$ 6	8 $\pm$ 1	8 $\pm$ 1	10 $\pm$ 8
MRT (h)	2 $\pm$ 0.5	6 $\pm$ 4	5 $\pm$ 1	5 $\pm$ 1	10 $\pm$ 11

<sup>†</sup> recombinant human LH, <sup>‡</sup> urinary human LH.

\* Parameters are: area under the concentration-time curve from time zero to infinity (AUC), maximal concentration (C<sub>max</sub>), total clearance (CL), renal clearance (CL<sub>r</sub>), initial half-life (t<sub>1/2 $\lambda_1$</sub> ), terminal half-life (t<sub>1/2</sub>), volume of distribution at steady-state (V<sub>ss</sub>), mean residence time (MRT).

Figure 1. Serum concentration-time profiles of LH immunoassay data after the IV administration of 300 (●), 10 000 (■) and 40 000 IU (▲) of recombinant human LH and 300 IU (○, dotted line) of urinary human LH (mean ± 1 SD, 12 down-regulated females) (Study 6135)



### Reviewer's Comments

- Sponsor mentions that there was an unexpected delay in the achievement of down-regulation mainly in the group that received 75 IU r-hLH (and to a lesser extent in a few subjects of the group receiving 300 IU r-hLH). Since the PK parameters were calculated following baseline adjustment, the PK profile/parameters are not most accurate following the 75 IU dose.
- The exposure (based on AUC) to r-hLH is proportional to the dose (between 75 – 40,000 IU).
- There are no apparent PK differences between the recombinant and urinary product following the 300 IU dose.
- This study used intravenous injection as the mode of administration. Luveris is designed to be used as a subcutaneous injection.

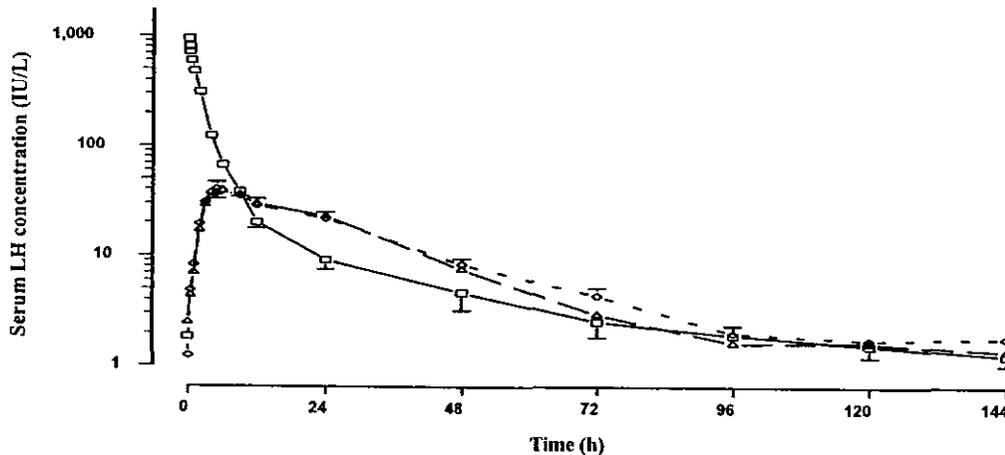
**Study 6136** was an open-label, random order, cross-over study conducted in twelve healthy female volunteers. The drug (r-hLH) was administered to each volunteer as a single dose (10,000 IU) on three occasions (IV, IM or SC) separated by a washout period of one week, according to an open, cross-over, random-order design. The administration of the study drug started, at the earliest, 10 days after the first SC administration of Goserelin, which took place on Day 1. The second administration of Goserelin took place on Day 28, if applicable. The first injection of r-hLH was given only if the volunteer was down-regulated, i.e. when her LH level was less than or equal to 3.0 IU/L. The study was composed of three treatments:

- 10,000 IU of r-hLH given by the IV route
- 10,000 IU of r-hLH given by the IM route
- 10,000 IU of r-hLH given by the SC route

Blood samples were drawn at the following time points: pre-dose, 30 min, 1, 2, 3, 4, 5, 6, 9, 12, 24, 48, 72, 96, 120 and 144 hours post dose. Serum LH concentrations were measured with an immunoradiometric assay (IRMA) and with an in vitro bioassay (Leydig Cell Bioassay). The measured LH concentrations versus time curves were analyzed for IV, IM, and SC administrations according to compartmental and non-compartmental pharmacokinetic analysis, after Goserelin down-regulation.

## Results:

**Figure 2.** Serum concentration of LH immunoassay concentrations versus time (log-linear plot) after single IV (solid line), IM (long-dashed line) and SC (short-dashed line) administrations of 10,000 IU of recombinant human LH (mean  $\pm$  1 SEM, 12 healthy down-regulated females) (Study 6136)



A two-compartment model was chosen for the IV dose, while a one-compartment model with zero-order absorption and a lag-time was chosen for fitting the IM and SC doses.

**Table 2.** Parameter estimates by modeling of LH pharmacokinetics (serum concentrations measured by the immunoassay and in vitro bioassay) after single IV, IM and SC administration in 12 female subjects (Study 6136)

PARAMETER (mean $\pm$ SD)	IMMUNOASSAY (estimated dose 5600 IU, nominal dose 10,000 IU)			IN VITRO BIOASSAY (estimated dose 10 280 IU, nominal dose 10,000 IU)		
	IV	IM	SC	IV	IM	SC
AUC (IU·h/L)	2 217 $\pm$ 500	1 118 $\pm$ 516	1 224 $\pm$ 480	4 472 $\pm$ 1 274	2 179 $\pm$ 672	2 466 $\pm$ 765
C <sub>0</sub> (IU/L)	863 $\pm$ 179	-	-	1 658 $\pm$ 222	-	-
C <sub>max</sub> (IU/L)	-	45 $\pm$ 20	41 $\pm$ 24	-	74 $\pm$ 28	72 $\pm$ 39
t <sub>max</sub> † (h)	-	9 (3-9)	5 (4-9)	-	6 (3-12)	5 (4-9)
CL (L/h)	2.6 $\pm$ 0.6	-	-	2.5 $\pm$ 0.6	-	-
t <sub>lag</sub> † (h)	-	0.4 (0-0.9)	0.2 (0-0.5)	-	0.3 (0-1.8)	0.1 (0-0.7)
$\tau$ (h)	-	5.0 $\pm$ 1.4	4.4 $\pm$ 1.2	-	4.3 $\pm$ 2.1	4.1 $\pm$ 1.5
t <sub>1/2<math>\lambda_1</math></sub> (h)	1.3 $\pm$ 0.3	-	-	1.0 $\pm$ 0.3	-	-
t <sub>1/2</sub> (h)	10 $\pm$ 5	16 $\pm$ 4	21 $\pm$ 5	19 $\pm$ 10	21 $\pm$ 6	24 $\pm$ 6
V <sub>ss</sub> (L)	14 $\pm$ 5	-	-	31 $\pm$ 15	-	-
MRT (h)	6 $\pm$ 3	-	-	15 $\pm$ 11	-	-
F (%)	-	54 $\pm$ 30	56 $\pm$ 23	-	51 $\pm$ 19	60 $\pm$ 20

† Median (range)

\*Concentration at time t=0 (C<sub>0</sub>), time to reach maximal concentration (t<sub>max</sub>), lag-time before absorption begins (t<sub>lag</sub>), zero order input duration ( $\tau$ ), bioavailability (F), area under the concentration-time curve from time zero to infinity (AUC), maximal concentration (C<sub>max</sub>), total clearance (CL), initial half-life (t<sub>1/2 $\lambda_1$</sub> ), terminal half-life (t<sub>1/2</sub>), volume of distribution at steady-state (V<sub>ss</sub>), mean residence time (MRT).

### Reviewer's Comments

- Approximately half of the administered drug is systemically available after IM or SC injection.
- PK parameters generally agreed between the two assay methods. However, there are some differences.
- No additional significance of this study is apparent in light of the fact that the actual intended dose (to be marketed) is 75 IU.

### Multiple Doses

**Study 6137** was a phase I study to assess the pharmacokinetics of r-hLH after single and repeated subcutaneous administration with or without r-hFSH (Gonal-F®) in 12 healthy female volunteers down regulated with Goserelin (Zoladex®). The study drugs (150 IU of r-hLH and r-hFSH) were administered (1) alone or in combination as a single SC injection, once per week separated by a period of one week in an open, cross-over, random-order design and (2) in combination once a day for seven days.

The objectives of the study were to assess the following in a healthy, down-regulated volunteer population:

- The pharmacokinetics of r-hLH with and without r-hFSH following SC administration of r-hLH.
- The pharmacokinetics of r-hFSH with and without r-hLH following SC administration of r-hFSH.
- The steady-state pharmacokinetics and pharmacodynamics following daily repeated SC administration of r-hLH combined with r-hFSH for one week.

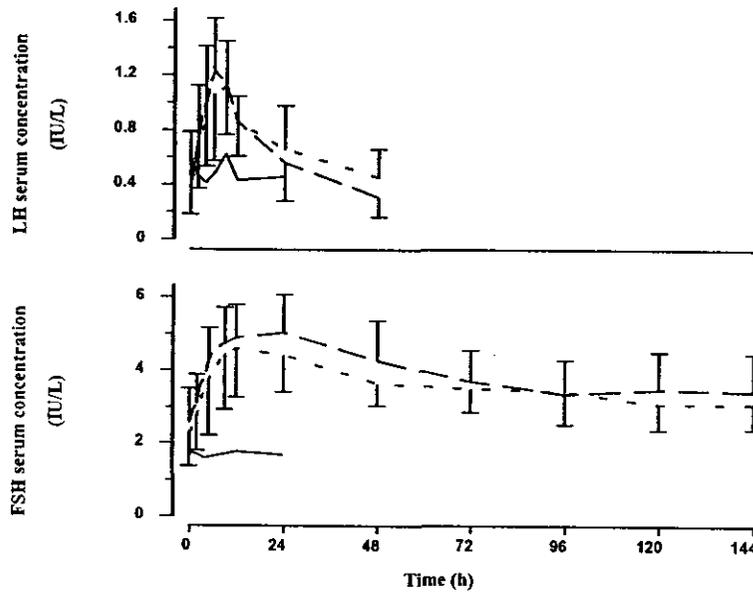
### Results:

**Table 3.** Mean ( $\pm$  SD) pharmacokinetic parameters of LH and FSH after single SC administration of 150 IU of recombinant human LH and FSH, given either alone or combined, in 12 subjects (Study 6137)

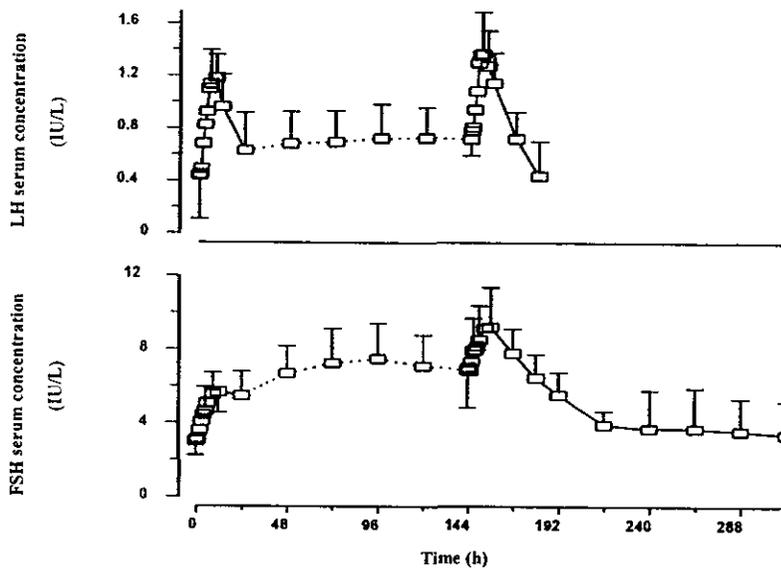
Drug administration	LH		FSH	
	alone	combined	alone	combined
<b>PK PARAMETER</b>				
AUC (IU·h/L)	44 $\pm$ 44	35 $\pm$ 15	274 $\pm$ 144	218 $\pm$ 125
C <sub>max</sub> (IU/L)	1.1 $\pm$ 0.3	1.0 $\pm$ 0.5	2.7 $\pm$ 0.9	2.5 $\pm$ 1.2
t <sub>max</sub> <sup>†</sup> (h)	6 (3-9)	6 (4-12)	24 (6-24)	18 (5-24)
t <sub>1/2</sub> (h)	1.9 $\pm$ 1.5	2.1 $\pm$ 1.0	4.9 $\pm$ 2.2	4.8 $\pm$ 7.8
t <sub>1/2</sub> (h)	14 $\pm$ 8	19 $\pm$ 8	59 $\pm$ 37	44 $\pm$ 26
Ae (IU)	0.4 $\pm$ 1.1	0.5 $\pm$ 1.2	13 $\pm$ 11	22 $\pm$ 22

<sup>†</sup> Median (range).

**Figure 3.** Concentrations of LH (upper panel) and FSH (lower panel) versus time during 24 hour baseline assessment (solid line) and after single SC administration of 150 IU of LH or FSH, respectively, either alone (long-dashed line) or in combination (short-dashed line); mean  $\pm$  1 SD, 12 healthy down-regulated females (Study 6137)



**Figure 4.** Concentrations of LH (upper panel) and FSH (lower panel) versus time following repeated daily SC administration over 7 days of 150 IU of recombinant human LH combined with 150 IU of recombinant human FSH (mean  $\pm$  1 SD, 12 down-regulated females) (Study 6137)



Note : Between 24 and 144 hours the line is dashed to reflect the fact that only trough levels are connected. Not all error bars are displayed.

**Table 4.** Mean ( $\pm$ SD) pharmacokinetic parameters of LH and FSH after repeated daily SC administration of 150 IU of recombinant human LH and 150 IU of recombinant human FSH in 12 down-regulated females (Study 6137)

Timing	LH		FSH	
	Day 1	Day 7	Day 1	Day 7
IMMUNODOSE (IU)	66		115	
PARAMETER*				
AUC <sub>0-24</sub> (IU·h/L)	15 $\pm$ 6	†22 $\pm$ 8	49 $\pm$ 23	†129 $\pm$ 47
C <sub>max</sub> (IU/L)	1.1 $\pm$ 0.3	1.3 $\pm$ 0.4	3.0 $\pm$ 1.2	6.4 $\pm$ 2.3
t <sub>max</sub> § (h)	6 (4-9)	† <sub>5</sub> (4-9)	12 (6-24)	† <sub>9</sub> (6-24)
T <sub>1/2λ<sub>1</sub></sub> (h)	3.9 $\pm$ 1.7		8.5 $\pm$ 2.8	
T <sub>1/2</sub> (h)	11 $\pm$ 5		16 $\pm$ 4	
R <sub>A</sub>	1.6 $\pm$ 0.8		2.9 $\pm$ 1.0	

\*Median (range).

†Value after the last dose (t = 144 hour) for repeated SC administration.

#### Reviewer's Comments

- C<sub>max</sub> of r-hLH following single doses of 150 IU was exceptionally lower in this study as compared to a previous single dose study (comparing Tables 1 and 3). Reason is unexplained. Other PK parameters were generally comparable between the two studies.
- Minor accumulation was observed for LH during the 7-day multiple dosing schedule. FSH showed higher accumulation.
- No apparent effect of FSH was detectable on the PK of LH (and vice versa). Sponsor performed statistical analysis (MANOVA) and concludes that there are no differences for both LH and FSH following single dose administration alone or in combination, indicating an absence of pharmacokinetic interaction between r-hLH and r-hFSH.
- In all the single and multiple dose studies submitted, PK profile and accurate parameters following the 75 IU SC dose (to be marketed) is not available probably because the dose is too low. However, PK parameters have been presented from immediate higher doses 150 and 300 IU.
- The combination of r-LH and r-FSH was administered as a *single* injection after dissolving 150 IU of each of the drug powders in 1 ml of water for injection.

#### **Q. Are there any other clinical pharmacology issues not addressed in this application?**

Luveris is indicated rarely in certain infertile, otherwise healthy women (during the age of fertility). The product is a recombinant form of an endogenous protein. Hence, issues such as metabolic drug interaction, intrinsic and extrinsic factors affecting clinical pharmacology and a formal PK-PD analysis of Luveris may not be relevant, and were not studied in this NDA. Independent clinical trials have been conducted in support of safety/efficacy.

**Biopharmaceutics**

*Q. Are the clinical and the to-be-marketed formulations same?*

No. The sponsor added [ ] (methionine) in the final product that is to be marketed that was absent in the clinical trial formulation. Additionally, the sponsor intends to [ ] Table 5 describes the to-be-marketed formulation:

**Table 1.**

Component	Function	Quantity
r-hLH	Active	3.7 µg* <sup>1</sup> (equivalent to 82.5 IU)
Sucrose, NF	/	47.75 mg
L-methionine, USP <sup>2</sup>		0.1 mg
Polysorbate 20, NF		0.05 mg
Disodium phosphate dihydrate, USP		0.825 mg
Sodium dihydrogen phosphate monohydrate, USP		0.052 mg
Phosphoric acid, concentrated, USP	pH-adjustment	q.s
Sodium hydroxide, USP	pH-adjustment	q.s.
[ ]		
Water for Injection, USP	Solvent for reconstitution	1 mL

\* [ ]  
 [ ] Water for Injection (see discussion below)  
<sup>1,2</sup> Changes made in the to-be-marketed formulation

The sponsor has submitted results of a traditional bioequivalence study to compare the clinical trial and the to-be-marketed formulations. Results show that these two are bioequivalent (below).

Study 22372 was a phase I, double-blind, cross-over study to assess the comparative bioavailability and the safety of two formulations of recombinant-human luteinizing hormone (r-hLH) administered subcutaneously in 34 healthy pituitary down-regulated premenopausal female volunteers.

Centralized analysis of serum and urine LH and FSH concentrations for this study, as well as the immunoactivity of the dose administered, was performed with the immunoradiometric assay [ ] This assay was conducted at [ ] The standard determination range was [ ] IU/L; the limit of detection (LOD) was [ ] IU/L and the limit of quantification (LOQ) was [ ] IU/L; the precision of the assay (%CV) was expected to be better than [ ] and was found to be [ ] With regard to the specificity of the kit, negligible cross-reactivities with FSH [ ] TSH [ ] and hCG [ ] were observed.

After the study was completed, the bio-analysis for LH measurements was repeated, because in the first bio-analysis both samples from single subjects were not always analysed in the same assay run.

In addition to the raw data, baseline corrected results were reported for information only as the correction had only a minor impact. The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-inf}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf(>60\%)}$  and  $AUC_{trun}$  were logarithmically transformed and subjected to a four-factor ANOVA (factors: treatment, period, treatment sequence and subject within sequence). Based upon the residual error of ANOVA, 90% Confidence Intervals for the ratio of geometric means of test and reference treatment were calculated.

Bioequivalence was to be concluded if the 90% Confidence Intervals for the ratio of geometric means of test and reference were included in the bioequivalence acceptance range (80-125%). For the pharmacokinetic parameter  $t_{max}$  a non-parametric Wilcoxon's method was used. In addition, an analogous, distribution-free Confidence Interval for the difference of test and reference was calculated.

### Results:

**Table 6.** Summary of the statistics on pharmacokinetic parameters of LH by treatment (new and current Luveris™ formulation) – Study 22372

Parameter	A: new	B: current	Point estimate Ratio new/current	90% CI range
$C_{max}$ (IU/L)	4.9 (1.8-15.5)	5.4 (1.4-11.3)	0.92	0.81-1.04
$t_{max}$ (h)*	9.0 [ 1 ]	8.0 [ 1 ]	1.0*	0.0-2.0
$t_{1/2}$ (h)	16.2 (6.6-56.5)	16.2 (6.4-46.8)	-	-
$AUC_{trun}$ (IUh/L)	79.2 (25.9-245.6)	89.1 (21.8-241.9)	0.90	0.84-0.97
$AUC_{0-last}$ (IUh/L)	83.3 (27.1-283.4)	97.0 (21.8-241.9)	0.88	0.79-0.98**
$AUC_{0-inf(>60\%)}$ (IUh/L)	140.5 (65.7-320.5)	145.3 (81.8-277.4)	1.00	0.88-1.14

\* Median (min-max)

\*\* 0.7853 - 0.9792

ANOVA revealed a significant period effect for  $C_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf(>60\%)}$  (both baseline and non-baseline corrected), and  $AUC_{trun}$  (non-baseline corrected). ANOVA revealed a significant treatment sequence effect for  $AUC_{0-inf}$  only in both baseline and non-baseline corrected data.

### Reviewer's Comments

- For all practical purposes, the two formulations are bioequivalent
- The new formulation is proposed to-be-marketed product, and this is acceptable.

## Analytical

A commercially available immunoradiometric assay [ ] was validated and used for centrally quantifying serum and urine levels of LH [ ] as well as FSH [ ] for the studies presented in this application (Studies 6135, 6136, 6137 and 22372). In addition, for Study 6136, a validated *in vitro* bioassay, the mouse Leydig tumor cell bioassay [ ] was also used in parallel so as to compare the levels of bioactive and immunoreactive LH.

The [ ] assay was validated by Serono and performed according to specifications except in the very high analyte concentrations where samples were diluted to bring the concentrations within the range covered by the kit standard curve.

Typically, the standard range for the LH immunoassay is [ ] IU/L, with an inter-assay coefficient of variation of [ ], intra-assay coefficient of variation of [ ] and limit of quantification of [ ] IU/L.

For each Phase I study, LH assay characteristics as performed by the sponsor laboratory can be summarized as showed in Table 7.

Table 7. Summary of LH assay characteristics for Serono Studies 6135, 6136, 6137, and 22372

	Study 6135	Study 6136	Study 6137	Study 22372
LOQ* (IU/L)	[ ]			[ ]
Serum LH interassay CV (%)				
Immunoassay	5.9-16.4	10	7.8-13	8.5-11.0%
Bioassay	NA	10	NA	NA
Urine LH CV (%)	2.6-10.8	NA	6.1-16.8	NA
Immunoassay				

\*Limit of Quantification

## Labeling

The following is an excerpt of the relevant sections of the proposed PPI for this product. In general, the labeling is acceptable. Minor changes are recommended (as below). Text to be deleted is marked with ~~strikeout~~ and additions are underlined.

### CLINICAL PHARMACOLOGY

The physicochemical, immunological, and biological activities of r-hLH are comparable to those of human pituitary and human menopausal urine-derived LH. In the ovaries, during the follicular phase, LH stimulates theca cells to secrete androgens, which will be used as the substrate by granulosa cell

2 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_\_ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

## Clinical Pharmacology & Biopharmaceutics Review

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**NDA:** 21-322

**Product Trade Name:** LUVERIS™ (lutropin alfa for injection)

**Active Ingredient/s:** Recombinant Human Luteinizing Hormone (r-hLH; 75 IU)

**Indication:** Induction of Ovulation (concomitant with r-hFSH)

**Submission Dates:** 5/12/2001 (original NDA); 12/17/01

**Sponsor:** Serono, Inc.

**Submission/Priority Type:** Original/3S

**Reviewer:** Dhruva J. Chatterjee, Ph.D.

**Team Leader:** Ameeta Parekh, Ph.D.

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## **Synopsis**

The subject of this submission, LUVERIS™ (lutropin alfa for injection) is composed of recombinant human luteinizing hormone, r-hLH. Lutropin alfa for injection is a heterodimeric glycoprotein consisting of two non-covalently linked subunits (designated  $\alpha$  and  $\beta$ ) of 92 and 121 amino acids, respectively. Luveris™ is a sterile, lyophilized powder intended for co-administration with 75 IU r-hFSH as a subcutaneous (sc) injection after reconstitution with Sterile Water for Injection, USP. The physicochemical, immunological, and biological activities of r-hLH are comparable to those of human pituitary and human menopausal urine-derived LH. Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. The main goal of therapy is the treatment of infertility and achievement of pregnancy.

## ***RECOMMENDATION***

From an OCPB perspective, the application is acceptable based on the data submitted. However, if LUVERIS is mixed with FSH products other than Gonal-F (the FSH product used in the studies supporting this NDA) prior to injection, please see comments below.

## ***COMMENTS TO MEDICAL OFFICER***

If this product labeling supports the mixing of LUVERIS with FSH products other than Gonal-F prior to injection, then the sponsor needs to address the effect of these other FSH products on the absorption and the PK profile of LUVERIS™ (and vice versa) prior to product approval.

## ***COMMENTS TO SPONSOR***

The sponsor is recommended to address how other marketed FSH product/s (based on dosage strength and formulation) may affect the absorption and the PK profile of LUVERIS™ (and vice versa) if the two are mixed prior to injection.

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On Original

## Overall Summary of Clinical Pharmacology and Biopharmaceutics Findings

- 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 parameters from the subcutaneous 75 IU dose (to be marketed product) due to the fact that the dose was low and baseline LH levels interfered in the analysis. However, PK profiles from immediate higher doses (150 and 300 IU) 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/safety.
- In 2 of the 3 submitted PK studies (Study 6137 and 21-322) where LUVERIS was administered as a subcutaneous injection, the site of injection was the abdomen (anterior abdominal wall).
- The intended to-be-marketed formulation is *not* exactly the same as the clinical trial formulation due to addition of 0.1 mg methionine [ ] in the final formulation. However, an adequate bioequivalence study was conducted and the results show that the two formulations are bioequivalent. Hence the change in formulation is acceptable and the new formulation may be marketed replacing the old (clinical trial) formulation.
- The intended use of Luveris is in combination with r-FSH. The label for Luveris directs dissolution of the contents of one vial of Luveris in 1 ml of water for injection followed by injection of this solution into the r-FSH powder. After mixing of these two powders, the final reconstituted solution is to be administered as a single injection. In the clinical trials, the r-LH and r-FSH were administered as two separate injections. In PK study 6137, the sponsor has provided PK data (for LH and FSH in 12 healthy females) following single 1-ml injections of a combination of r-LH and r-FSH.
- Due to the nature of how Luveris is intended to be administered, the final injectable formulation is a solution containing all constituents of the Luveris formulation *and* that of the particular r-hFSH product used. In this NDA, the sponsor evaluated the combination of Luveris with one specific marketed brand of r-FSH, and have not presented any information/theories as to how other marketed r-hFSH product/s (either available currently or in the future) may affect the absorption and the PK profile of Luveris (and vice versa), if the two products are mixed prior to injection. It is critical that the sponsor addresses this issue in a timely manner.

## Background

### *Questions addressed in this section:*

*What are the highlights of chemistry and formulation of the drug and drug product?*

*What is the mechanism of action, proposed indication and main goal of therapy?*

*What are other drugs available in this class, and what is its foreign marketing history?*

The subject of this submission, LUVERIS™ (lutropin alfa for injection) is composed of recombinant human luteinizing hormone, r-hLH. Lutropin alfa for injection is a heterodimeric glycoprotein consisting of two non-covalently linked subunits (designated  $\alpha$  and  $\beta$ ) of 92 and 121 amino acids, respectively. The carbohydrate chain attachment to the r-hLH protein core occurs via N- but not O-linkage. The N glycosylation sites are Asn-52 and Asn-78 for the  $\alpha$ -subunit and Asn-30 for the  $\beta$ -subunit. The primary structure of the  $\alpha$  - chain of r-hLH is identical to that of the  $\alpha$  - chain of hCG, FSH and TSH. The glycoform pattern of the  $\alpha$  - subunit of r-hLH is closely comparable to pituitary derived hLH, the differences mainly being due to the branching and sialylation extent of the oligosaccharides. The  $\beta$  - chain has an N-glycosylation site and its structure and glycosylation pattern are very similar to that of pituitary-derived hLH.

Luveris™ is a sterile, lyophilized powder intended for co-administration with r-hFSH as a subcutaneous (sc) injection after reconstitution with Sterile Water for Injection, USP. Each vial of Luveris™ contains 82.5 IU lutropin alfa, 48 mg sucrose, 0.83 mg dibasic sodium phosphate dihydrate, 0.052 mg monobasic sodium phosphate monohydrate, 0.05 mg polysorbate 20, 0.1 mg L-methionine and phosphoric acid and/or sodium hydroxide to adjust the pH. After reconstitution with one vial of enclosed diluent, the product will deliver 75 IU of recombinant human luteinizing hormone. The pH of the reconstituted solution is 7.5 to 8.5.

The physicochemical, immunological, and biological activities of r-hLH are comparable to those of human pituitary and human menopausal urine-derived LH. In the ovaries, during the follicular phase, LH stimulates theca cells to secrete androgens that is used as the substrate by granulosa cell aromatase enzyme to produce estradiol, supporting Follicle-Stimulating Hormone (FSH)-induced follicular development. Luveris™ is administered concomitantly with r-hFSH to stimulate development of a competent follicle and to indirectly prepare the reproductive tract for implantation and pregnancy.

Luveris™ (lutropin alfa for injection) is indicated for concomitant administration with r-hFSH for the induction of ovulation in infertile women with severe LH deficiency. The main goal of therapy is the treatment of infertility and achievement of pregnancy. It should be noted here that this NDA is seeking approval for this product for an orphan indication.

Serono Inc., has recently been granted marketing authorization for the recombinant LH product in several countries including the European Union. However, as of January 2001, this product has not been marketed in any country. This is the first application seeking approval for a purified 'LH-only' product for this current indication. Combination of LH and FSH is available as menotropins for injections for many years. Purified recombinant human FSH (Gonal F and Follistim) is available as an 'FSH-only' product.

## Clinical Pharmacology

### *Q. What are the single and multiple dose pharmacokinetic properties of r-hLH?*

#### Single Dose

**Study 6135** was a phase I study to assess the pharmacokinetics of recombinant-human luteinizing hormone (r-hLH) after single IV administration of increasing doses compared to a single dose of Pergonal® (hMG) in 12 healthy female volunteers down regulated with Goserelin (Zoladex®).

The primary PK objectives of this study were:

- To assess the pharmacokinetic characteristics and linearity of r-hLH following IV administration of two low (75 and 300 IU) and two high (10,000 and 40,000 IU) doses injected to 12 healthy female volunteers.
- To compare the pharmacokinetics of r-hLH with that of u-hLH contained in the hMG preparation (Pergonal® 300 IU of u-hLH and 300 IU of u-hFSH) following a single IV injection.

Blood samples were collected at the following time-points: 0 (pre-dose), 5 min, 10 min, 30 min, 1, 2, 4, 6, 9, 12, 24, 48, and 72 h, and up to 144 h for the two high doses. Urine samples were also collected during the following time intervals post-dose: 0-2h, 2-6h, 6-12h, 12-36h, and 36-60h.

#### **Results:**

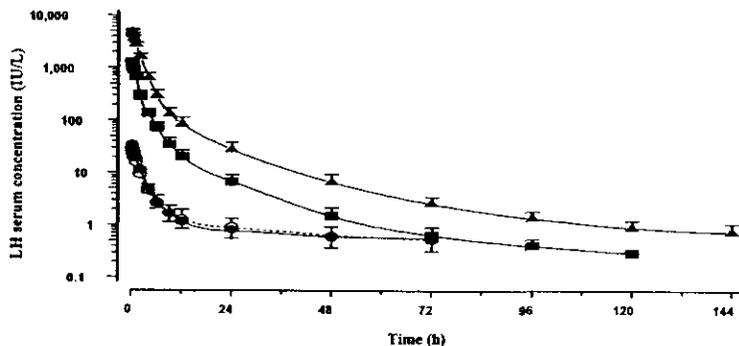
**Table 1.** Model-dependent pharmacokinetic estimates obtained after increasing IV r-hLH doses administered to healthy pre-menopausal down-regulated females (Study 6135, mean  $\pm$  SD) (n=12)

Parameters*	r-hLH <sup>†</sup>				u-hLH <sup>‡</sup>
	75	300	10,000	40,000	300
Nominal Dose (IU)	75	300	10,000	40,000	300
Immunocontent (IU)	33	132	4 560	18 240	87
AUC (IU·h/L)	13 $\pm$ 4	84 $\pm$ 14	2 625 $\pm$ 421	11 089 $\pm$ 1 711	80 $\pm$ 20
C <sub>max</sub> (IU/L)	7 $\pm$ 2	35 $\pm$ 6	1 221 $\pm$ 200	4 744 $\pm$ 535	27 $\pm$ 5
CL (L/h)	3 $\pm$ 2	1.6 $\pm$ 0.3	1.8 $\pm$ 0.3	1.7 $\pm$ 0.3	1.2 $\pm$ 0.3
CL <sub>renal</sub> (L/h)	0.12	0.03 $\pm$ 0.03	0.06 $\pm$ 0.02	0.05 $\pm$ 0.01	0.33 $\pm$ 0.22
t <sub>1/2<math>\lambda_1</math></sub> (h)	1.1 $\pm$ 0.2	1.2 $\pm$ 0.2	1.2 $\pm$ 0.2	1.3 $\pm$ 0.2	1.2 $\pm$ 0.2
t <sub>1/2</sub> (h)	NA	11 $\pm$ 8	9 $\pm$ 2	11 $\pm$ 1	12 $\pm$ 12
V <sub>ss</sub> (L)	5 $\pm$ 3	10 $\pm$ 6	8 $\pm$ 1	8 $\pm$ 1	10 $\pm$ 8
MRT (h)	2 $\pm$ 0.5	6 $\pm$ 4	5 $\pm$ 1	5 $\pm$ 1	10 $\pm$ 11

<sup>†</sup> recombinant human LH, <sup>‡</sup> urinary human LH.

\* Parameters are: area under the concentration-time curve from time zero to infinity (AUC), maximal concentration (C<sub>max</sub>), total clearance (CL), renal clearance (CL<sub>r</sub>), initial half-life (t<sub>1/2 $\lambda_1$</sub> ), terminal half-life (t<sub>1/2</sub>), volume of distribution at steady-state (V<sub>ss</sub>), mean residence time (MRT).

Figure 1. Serum concentration-time profiles of LH immunoassay data after the IV administration of 300 (●), 10 000 (■) and 40 000 IU (▲) of recombinant human LH and 300 IU (○, dotted line) of urinary human LH (mean ± 1 SD, 12 down-regulated females) (Study 6135)



### Reviewer's Comments

- Sponsor mentions that there was an unexpected delay in the achievement of down-regulation mainly in the group that received 75 IU r-hLH (and to a lesser extent in a few subjects of the group receiving 300 IU r-hLH). Since the PK parameters were calculated following baseline adjustment, the PK profile/parameters are not most accurate following the 75 IU dose.
- The exposure (based on AUC) to r-hLH is proportional to the dose (between 75 – 40,000 IU).
- There are no apparent PK differences between the recombinant and urinary human LH product following the 300 IU dose.
- This study used intravenous injection as the mode of administration. Luveris is designed to be used as a subcutaneous injection.

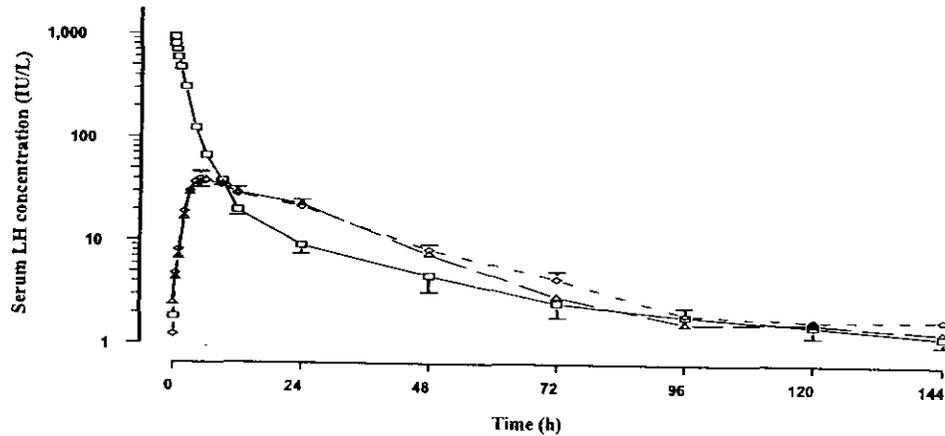
**Study 6136** was an open-label, random order, cross-over study conducted in twelve healthy female volunteers. The drug (r-hLH) was administered to each volunteer as a single dose (10,000 IU) on three occasions (IV, IM or SC) separated by a washout period of one week, according to an open, cross-over, random-order design. The administration of the study drug started, at the earliest, 10 days after the first SC administration of Goserelin, which took place on Day 1. The second administration of Goserelin took place on Day 28, if applicable. The first injection of r-hLH was given only if the volunteer was down-regulated, i.e. when her LH level was less than or equal to 3.0 IU/L. The study was composed of three treatments:

- 10,000 IU of r-hLH given by the IV route
- 10,000 IU of r-hLH given by the IM route
- 10,000 IU of r-hLH given by the SC route

Blood samples were drawn at the following time points: pre-dose, 30 min, 1, 2, 3, 4, 5, 6, 9, 12, 24, 48, 72, 96, 120 and 144 hours post dose. Serum LH concentrations were measured with an immunoradiometric assay [ ] and with an in vitro bioassay [ ] (Leydig Cell Bioassay). The measured LH concentrations versus time curves were analyzed for IV, IM, and SC administrations according to compartmental and non-compartmental pharmacokinetic analysis, after Goserelin down-regulation.

## Results:

**Figure 2.** Serum concentration of LH immunoassay concentrations versus time (log-linear plot) after single IV (solid line), IM (long-dashed line) and SC (short-dashed line) administrations of 10,000 IU of recombinant human LH (mean  $\pm$  1 SEM, 12 healthy down-regulated females) (Study 6136)



A two-compartment model was chosen for the IV dose, while a one-compartment model with zero-order absorption and a lag-time was chosen for fitting the IM and SC doses.

**Table 2.** Parameter estimates by modeling of LH pharmacokinetics (serum concentrations measured by the immunoassay and in vitro bioassay) after single IV, IM and SC administration in 12 female subjects (Study 6136)

PARAMETER (mean $\pm$ SD)	IMMUNOASSAY (estimated dose 5600 IU, nominal dose 10,000 IU)			IN VITRO BIOASSAY (estimated dose 10 280 IU, nominal dose 10,000 IU)		
	IV	IM	SC	IV	IM	SC
AUC (IU·h/L)	2 217 $\pm$ 500	1 118 $\pm$ 516	1 224 $\pm$ 480	4 472 $\pm$ 1 274	2 179 $\pm$ 672	2 466 $\pm$ 765
C <sub>0</sub> (IU/L)	863 $\pm$ 179	-	-	1 658 $\pm$ 222	-	-
C <sub>max</sub> (IU/L)	-	45 $\pm$ 20	41 $\pm$ 24	-	74 $\pm$ 28	72 $\pm$ 39
t <sub>max</sub> <sup>†</sup> (h)	-	9 (3-9)	5 (4-9)	-	6 (3-12)	5 (4-9)
CL (L/h)	2.6 $\pm$ 0.6	-	-	2.5 $\pm$ 0.6	-	-
t <sub>lag</sub> <sup>†</sup> (h)	-	0.4 (0-0.9)	0.2 (0-0.5)	-	0.3 (0-1.8)	0.1 (0-0.7)
$\tau$ (h)	-	5.0 $\pm$ 1.4	4.4 $\pm$ 1.2	-	4.3 $\pm$ 2.1	4.1 $\pm$ 1.5
t <sub>1/2<math>\alpha</math></sub> (h)	1.3 $\pm$ 0.3	-	-	1.0 $\pm$ 0.3	-	-
t <sub>1/2<math>\beta</math></sub> (h)	10 $\pm$ 5	16 $\pm$ 4	21 $\pm$ 5	19 $\pm$ 10	21 $\pm$ 6	24 $\pm$ 6
V <sub>ss</sub> (L)	14 $\pm$ 5	-	-	31 $\pm$ 15	-	-
MRT (h)	6 $\pm$ 3	-	-	15 $\pm$ 11	-	-
F (%)	-	54 $\pm$ 30	56 $\pm$ 23	-	51 $\pm$ 19	60 $\pm$ 20

<sup>†</sup> Median (range)

\*Concentration at time t=0 (C<sub>0</sub>), time to reach maximal concentration (t<sub>max</sub>), lag-time before absorption begins (t<sub>lag</sub>), zero order input duration ( $\tau$ ), bioavailability (F), area under the concentration-time curve from time zero to infinity (AUC), maximal concentration (C<sub>max</sub>), total clearance (CL), initial half-life (t<sub>1/2 $\alpha$</sub> ), terminal half-life (t<sub>1/2 $\beta$</sub> ), volume of distribution at steady-state (V<sub>ss</sub>), mean residence time (MRT).

### Reviewer's Comments

- Absolute bioavailability of the IM and SC injections was approximately 50-60%.
- PK parameters generally agreed between the two assay methods. However, there are some differences.
- No additional significance of this study is apparent in light of the fact that the actual intended dose (to be marketed) is 75 IU.

### Multiple Doses

**Study 6137** was a phase I study to assess the pharmacokinetics of r-hLH after single and repeated subcutaneous administration with or without r-hFSH (Gonal-F®) in 12 healthy female volunteers down regulated with Goserelin (Zoladex®). The study drugs (150 IU of r-hLH and r-hFSH) were administered (1) alone or in combination as a single SC injection, once per week separated by a period of one week in an open, cross-over, random-order design and (2) in combination once a day for seven days.

The objectives of the study were to assess the following in a healthy, down-regulated volunteer population:

- The pharmacokinetics of r-hLH with and without r-hFSH following SC administration of r-hLH.
- The pharmacokinetics of r-hFSH with and without r-hLH following SC administration of r-hFSH.
- The steady-state pharmacokinetics and pharmacodynamics following daily repeated SC administration of r-hLH combined with r-hFSH for one week.

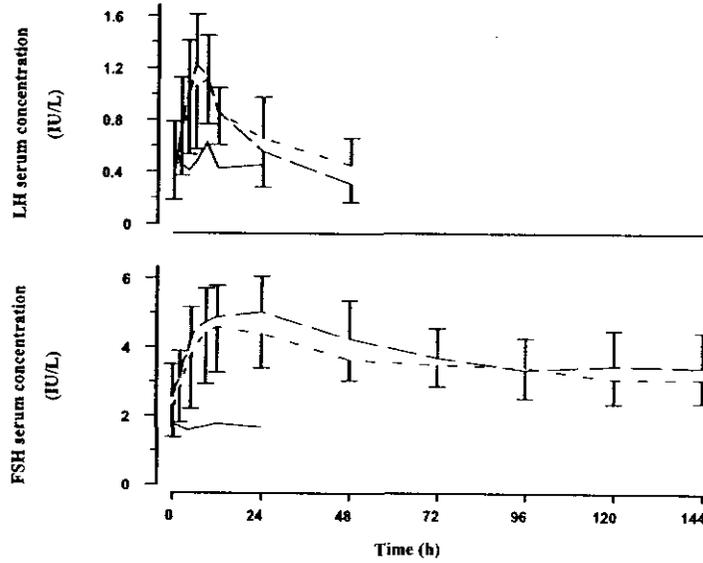
### Results:

**Table 3.** Mean ( $\pm$  SD) pharmacokinetic parameters of LH and FSH after single SC administration of 150 IU of recombinant human LH and FSH, given either alone or combined, in 12 subjects (Study 6137)

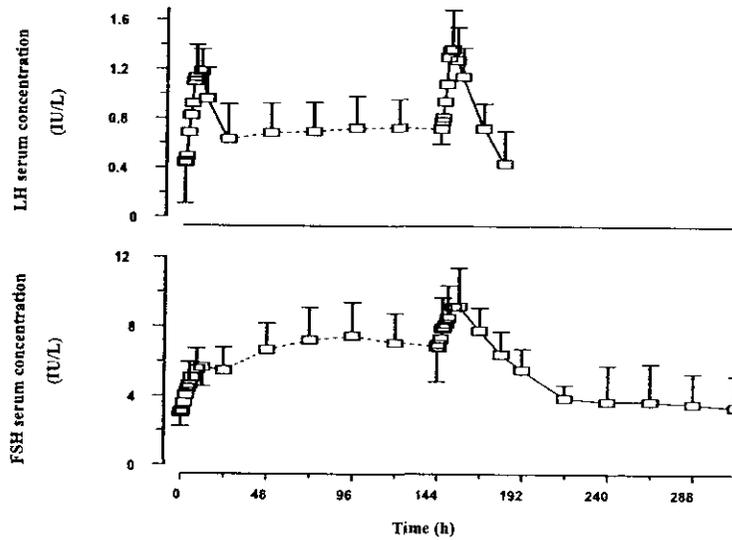
Drug administration	LH		FSH	
	alone	combined	alone	combined
<b>PK PARAMETER</b>				
AUC (IU·h/L)	44 $\pm$ 44	35 $\pm$ 15	274 $\pm$ 144	218 $\pm$ 125
C <sub>max</sub> (IU/L)	1.1 $\pm$ 0.3	1.0 $\pm$ 0.5	2.7 $\pm$ 0.9	2.5 $\pm$ 1.2
t <sub>max</sub> <sup>†</sup> (h)	6 (3-9)	6 (4-12)	24 (6-24)	18 (5-24)
t <sub>1/2λ1</sub> (h)	1.9 $\pm$ 1.5	2.1 $\pm$ 1.0	4.9 $\pm$ 2.2	4.8 $\pm$ 7.8
t <sub>1/2</sub> (h)	14 $\pm$ 8	19 $\pm$ 8	59 $\pm$ 37	44 $\pm$ 26
Ae (IU)	0.4 $\pm$ 1.1	0.5 $\pm$ 1.2	13 $\pm$ 11	22 $\pm$ 22

<sup>†</sup> Median (range).

**Figure 3.** Concentrations of LH (upper panel) and FSH (lower panel) versus time during 24 hour baseline assessment (solid line) and after single SC administration of 150 IU of LH or FSH, respectively, either alone (long-dashed line) or in combination (short-dashed line); mean  $\pm$  1 SD, 12 healthy down-regulated females (Study 6137)



**Figure 4.** Concentrations of LH (upper panel) and FSH (lower panel) versus time following repeated daily SC administration over 7 days of 150 IU of recombinant human LH combined with 150 IU of recombinant human FSH (mean  $\pm$  1 SD, 12 down-regulated females) (Study 6137)



Note : Between 24 and 144 hours the line is dashed to reflect the fact that only trough levels are connected. Not all error bars are displayed.

**Table 4.** Mean ( $\pm$ SD) pharmacokinetic parameters of LH and FSH after repeated daily SC administration of 150 IU of recombinant human LH and 150 IU of recombinant human FSH in 12 down-regulated females (Study 6137)

Timing	LH		FSH	
	Day 1	Day 7	Day 1	Day 7
IMMUNODOSE (IU)	66		115	
PARAMETER*				
AUC <sub>0-24</sub> (IU·h/L)	15 $\pm$ 6	†22 $\pm$ 8	49 $\pm$ 23	†129 $\pm$ 47
C <sub>max</sub> (IU/L)	1.1 $\pm$ 0.3	1.3 $\pm$ 0.4	3.0 $\pm$ 1.2	6.4 $\pm$ 2.3
t <sub>max</sub> § (h)	6 (4-9)	†5 (4-9)	12 (6-24)	†9 (6-24)
T <sub>1/2</sub> λ <sub>1</sub> (h)	3.9 $\pm$ 1.7		8.5 $\pm$ 2.8	
T <sub>1/2</sub> (h)	11 $\pm$ 5		16 $\pm$ 4	
R <sub>A</sub>	1.6 $\pm$ 0.8		2.9 $\pm$ 1.0	

\*Median (range).

† Value after the last dose (t = 144 hour) for repeated SC administration.

#### Reviewer's Comments

- Minor accumulation was observed for LH during the 7-day multiple dosing schedule. FSH showed higher accumulation.
- No apparent effect of FSH was detectable on the PK of LH (and vice versa). Sponsor performed statistical analysis (MANOVA) and concludes that there are no differences for both LH and FSH following single dose administration alone or in combination, indicating an absence of pharmacokinetic interaction between r-hLH and r-hFSH.
- In all the single and multiple dose studies submitted, PK profile and accurate parameters following the 75 IU SC dose (to be marketed) is not available probably because the dose is too low. However, PK parameters have been presented from immediate higher doses 150 and 300 IU.
- The combination of r-LH and r-FSH was administered as a *single* injection after dissolving 150 IU of each of the drug powders in 1 ml of water for injection.

#### Q. Are there any other clinical pharmacology issues not addressed in this application?

Based on limited dose finding information submitted in the clinical section of the NDA, the medical officer believes that the sponsor might not have selected the lowest effective dose (75 IU) for the Phase 3 trials. According to the medical officer's review, there were some incidences of ovarian hyperstimulation (an adverse event) associated with the 75 IU dose in the phase 3 clinical trials.

Luveris is indicated rarely in certain infertile, otherwise healthy women (during the age of fertility). The product is a recombinant form of an endogenous protein. Hence, issues such as metabolic drug interaction, intrinsic and extrinsic factors affecting clinical pharmacology and a

formal PK-PD analysis of Luveris may not be relevant, and were not studied in this NDA. Independent clinical trials have been conducted in support of safety/efficacy.

## Biopharmaceutics

### Q. Are the clinical and the to-be-marketed formulations same?

No. The sponsor added L (methionine) in the final product that is to be marketed that was absent in the clinical trial formulation. Additionally, the sponsor intends L the to-be-marketed formulation: J Table 5 describes

Table 1.

Component	Function	Quantity
r-hLH	Active	3.7 $\mu\text{g}^{*1}$ (equivalent to 82.5 IU)
Sucrose, NF		47.75 mg
L-methionine, USP <sup>2</sup>		0.1 mg
Polysorbate 20, NF		0.05 mg
Disodium phosphate dihydrate, USP		0.825 mg
Sodium dihydrogen phosphate monohydrate, USP		0.052 mg
Phosphoric acid, concentrated, USP	pH-adjustment	q.s
Sodium hydroxide, USP	pH-adjustment	q.s.
Water for Injection, USP	Solvent for reconstitution	1 mL

\* 1.

J Water for Injection (see discussion below)

<sup>1,2</sup> Changes made in the to-be-marketed formulation

The sponsor has submitted results of a traditional bioequivalence study to compare the clinical trial and the to-be-marketed formulations. Results show that these two are bioequivalent (below).

Study was a phase I, double-blind, cross-over study to assess the comparative bioavailability and the safety of two formulations of recombinant-human luteinizing hormone (r-hLH) administered subcutaneously in 34 healthy pituitary down-regulated premenopausal female volunteers. 'A' is the to be marketed (new) formulation and 'B' is the clinical trial (current) formulation.

Centralized analysis of serum and urine LH and FSH concentrations for this study, as well as the immunoactivity of the dose administered, was performed with the immunoradiometric assay L

J This assay was conducted at L J The standard determination range was — IU/L; the limit of detection (LOD) was — IU/L and

the limit of quantification (LOQ) was  $\sim$  IU/L; the precision of the assay (%CV) was expected to be better than  $\sim$  and was found to be  $\sim$ . With regard to the specificity of the kit, negligible cross-reactivities with FSH ( $\sim$ ), TSH ( $\sim$ ) and hCG ( $\sim$ ) were observed. Baseline corrected results were also reported for information only. The pharmacokinetic parameters  $C_{max}$ ,  $AUC_{0-inf}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf(>60\%)}$  and  $AUC_{trun}$  were logarithmically transformed and subjected to a four-factor ANOVA (factors: treatment, period, treatment sequence and subject within sequence). Based upon the residual error of ANOVA, 90% Confidence Intervals for the ratio of geometric means of test and reference treatment were calculated.

Bioequivalence was to be concluded if the 90% Confidence Intervals for the ratio of geometric means of test and reference were included in the bioequivalence acceptance range (80-125%). For the pharmacokinetic parameter  $t_{max}$  a non-parametric Wilcoxon's method was used. In addition, an analogous, distribution-free Confidence Interval for the difference of test and reference was calculated.

#### Results:

**Table 6.** Summary of the statistics on pharmacokinetic parameters of LH by treatment (new and current Luveris™ formulation) – Study 22372

Parameter	A: new	B: current	Point estimate Ratio new/current	90% CI range
$C_{max}$ (IU/L)	4.9 (1.8-15.5)	5.4 (1.4-11.3)	0.92	0.81-1.04
$t_{max}$ (h)*	9.0 ( )	8.0 ( )	1.0*	0.0-2.0
$t_{1/2}$ (h)	16.2 (6.6-56.5)	16.2 (6.4-46.8)	-	-
$AUC_{trun}$ (IU·h/L)	79.2 (25.9-245.6)	89.1 (21.8-241.9)	0.90	0.84-0.97
$AUC_{0-last}$ (IU·h/L)	83.3 (27.1-283.4)	97.0 (21.8-241.9)	0.88	0.79-0.98**
$AUC_{0-inf(>60\%)}$ (IU·h/L)	140.5 (65.7-320.5)	145.3 (81.8-277.4)	1.00	0.88-1.14

\* Median (min-max)

\*\* 0.7853 - 0.9792

ANOVA revealed a significant period effect for  $C_{max}$ ,  $AUC_{0-last}$ ,  $AUC_{0-inf(>60\%)}$  (both baseline and non-baseline corrected), and  $AUC_{trun}$  (non-baseline corrected). ANOVA revealed a significant treatment sequence effect for  $AUC_{0-inf}$  only in both baseline and non-baseline corrected data.

#### Reviewer's Comments

- The two formulations are bioequivalent with respect to  $C_{max}$  and  $AUC_{0-inf}$ .
- The new formulation is the proposed to-be-marketed product, and this is acceptable.

#### Analytical

A commercially available immunoradiometric assay (L) was validated and used for centrally quantifying serum and urine levels of LH (L) as well as FSH (L) for the studies presented in this application (Studies 6135, 6136, 6137 and 22372). In addition, for Study 6136, a validated *in vitro* bioassay, the mouse Leydig tumor cell bioassay (L) was also used in parallel so as to compare the levels of bioactive and immunoreactive LH.

The (L) assay was validated by Serono and performed according to specifications except in the very high analyte concentrations where samples were diluted to bring the concentrations within the range covered by the kit standard curve.

Typically, the standard range for the LH immunoassay is (L) IU/L, with an inter-assay coefficient of variation of (L), intra-assay coefficient of variation of (L) and limit of quantification of (L) IU/L.

For each Phase I study, LH assay characteristics as performed by the sponsor laboratory can be summarized as showed in Table 7.

**Table 7.** Summary of LH assay characteristics for Serono Studies 6135, 6136, 6137, and 22372

	Study 6135	Study 6136	Study 6137	Study 22372
<b>LOQ* (IU/L)</b>	(L)			(L)
<b>Serum LH interassay CV (%)</b>				
<b>Immunoassay</b>	5.9-16.4	10	7.8-13	8.5-11.0%
<b>Bioassay</b>	NA	10	NA	NA
<b>Urine LH CV (%)</b>	2.6-10.8	NA	6.1-16.8	NA
<b>Immunoassay</b>				

\*Limit of Quantification

## Labeling

The following is an excerpt of the relevant sections of the proposed PPI for this product. In general, the labeling is acceptable. Minor changes are recommended (as below). Text to be deleted is marked with ~~strikeout~~ and additions are underlined.

### CLINICAL PHARMACOLOGY

The physicochemical, immunological, and biological activities of r-hLH are comparable to those of human pituitary and human menopausal urine-derived LH. In the ovaries, during the follicular phase, LH stimulates theca cells to secrete androgens, which will be used as the substrate by granulosa cell aromatase enzyme to produce estradiol, supporting Follicle-Stimulating Hormone (FSH)-induced follicular development. Luveris™ is administered concomitantly with r-hFSH to stimulate development of a competent follicle and to indirectly prepare the reproductive tract for implantation and pregnancy.

**Pharmacokinetics**

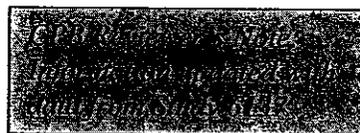
When given by intravenous administration, r-hLH demonstrates linear pharmacokinetics over the 300 to 40,000 IU dose range. Following a 75 IU dose, the concentration range is too small to allow proper quantification of the pharmacokinetic parameters. The disposition of r-hLH is adequately described by a biexponential model.  $\square$

3

Following subcutaneous administration, the terminal half-life is slightly longer than after intravenous administration. Upon repeated daily administration, a modest accumulation takes place (accumulation ratio of  $1.6 \pm 0.8$ ). Following administration of a higher dose of Luveris™ — r-hLH pharmacokinetics are described in Table 1.

**Table 2: Pharmacokinetic parameters† (mean ± SD) of r-hLH after single-dose SC administration of Luveris™ in pituitary desensitized healthy female volunteers**

Parameter†	Luveris™ — 150 IU SC
$C_{max}$ (IU/L)	— $1.1 \pm 0.3$
$t_{max}$ (h)‡	— $6 (3-9)$
$AUC_{inf}$ (h·IU/L)	— $44 \pm 44$
$t_{1/2}$ (h)	— $14 \pm 8$



†  $C_{max}$ : peak concentration,  $t_{max}$ : time of  $C_{max}$ , AUC: total area under the curve,  $t_{1/2}$ : elimination half-life, ‡ median (range)

**Absorption**

Following subcutaneous administration of Luveris™, maximum serum concentration is reached after approximately 4 to 16 hours.

The mean absolute bioavailability of Luveris™ following a single subcutaneous injection (at a much higher dose to allow proper quantification, i.e. 10,000 IU) to healthy female volunteers is about  $56 \pm 23\%$ , supported by  $\square$   $\square$  immunoassay method. There were no statistical differences between the intramuscular and subcutaneous routes of administration for  $C_{max}$ ,  $t_{max}$ , or bioavailability.

**Distribution**

Following an intravenous dose of 300 IU, a rapid distribution phase ( $t_{1/2 \lambda 1}$  of approximately 1 hour);  $\square$   $\square$  and a terminal half-life of approximately — 11 hours was observed for r-hLH.

The steady state volume of distribution ( $V_{ss}$ ) was approximately  $\sim 10 L$ .

Mean residence time (MRT) was around  $\sim 6$  hours.

#### *Metabolism/Excretion*

Following subcutaneous administration of Luveris™, r-hLH is eliminated from the body with a mean terminal half-life of about 18 hours. Total body clearance is approximately 2 to 3 L/h with less than 5 percent of the dose being excreted unchanged renally.

#### *Pharmacodynamics*

In the stimulation of follicular development, the primary effect resulting from administration of Luveris™ is an increase in estradiol secretion by the follicles, the growth of which is stimulated by FSH.

#### *Special populations*

Pharmacokinetics of Luveris™ in the geriatric or pediatric population, or in patients with renal or hepatic insufficiency have not been established.

#### *Drug-Drug Interactions*

There is no pharmacokinetic interaction with r-hFSH when administered simultaneously. No drug-drug interaction studies have been conducted.

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