CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 21047

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Moore

AUG 11 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**21-047**
Compound:	Menotropins (SC Repronex™, 75 IU FSH + 75 IU LH)
Sponsor:	Ferring Pharmaceuticals, Inc.
Type of Submission:	New Drug Product
Date of Submission:	October 26, 1998
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.
Pharmacometrics Consult:	Michael J. Fossler, Pharm.D., Ph.D.

Background

Intramuscular injection (IM) Repronex™ is approved (ANDA 73-598/599) as equivalent to IM Pergonal® for the induction of ovulation, in vitro fertilization (IVF), and spermatogenesis (SG). This 505 (b)(2) NDA seeks approval of subcutaneous injection (SC) Repronex™ for the same indications as IM Repronex™, except SG. The sponsor also markets menotropins as IM Menogon® in Europe. Menogon® and Repronex™ are sourced from the same bulk active drug product and contain 75 IU follicle stimulating hormone (FSH) and 75 IU luteinizing hormone (LH) per ampule. However, Menogon® contains less lactose than Repronex™ (5 versus 20 mg per ampule) and is manufactured at different facilities (Kiel, Germany and Puerto Rico, respectively). The formulations for SC Repronex™ and IM Repronex™ are identical. The sponsor conducted 2 clinical pharmacology and biopharmaceutics studies (Meno 96/02/NL and FPI REP 97-01).

The following questions, based on the content of this NDA, guided this review.

1. What are menotropins?

Menotropins are urinary human menopausal gonadotropins (HMG), which contain equal amounts of FSH and LH. FSH and LH are anterior pituitary glycoproteins. FSH and LH have 2 nonidentical and noncovalently linked peptide subunits (α and β). The α subunit of each hormone is nearly identical. The biological specificity resides in the β subunit.

2. How do menotropins work?

FSH binds to the granulosa cells to stimulate follicular growth and maturation. FSH acts on the seminiferous tubules to initiate SG. FSH stimulates the induction of aromatase systems of the granulosa cells for the aromatization of androgens to estrogen. LH facilitates follicular estrogen biosynthesis and stimulates thecal androgen production.

3. What are the proposed indications for SC Repronex™?

Same as IM Repronex™, except SG (no male patients were studied for this NDA).

Menotropins and human chorionic gonadotropin (hCG) given in a sequential manner are indicated for the induction of ovulation and pregnancy in the anovulatory infertile patient, in whom the cause of anovulation is functional and is not due to primary ovarian failure. Menotropins and hCG may also be used to stimulate the development of multiple follicles in ovulatory patients participating in an IVF program.

4. What are the adverse effects of menotropins in women?

Gonadotropins are the most potent follicular growth stimulants available. Adverse effects include ovarian hyperstimulation syndrome (OHSS), multiple pregnancies, and early pregnancy loss. The incidence of OHSS varies from 8 to 23% in mild, <1 to 7% in moderate, and 1 to 1.8% in severe form. Severe OHSS manifests as ascites, pleural effusions, hypercoagulability, and thromboembolism, which require hospitalization. OHSS occurs in 0.4% of patients treated with ≤ 150 IU menotropins and in 1.3% of patients treated with > 150 IU menotropins. The incidence of multiple pregnancies and early pregnancy loss are 10 to 40% and 25%, respectively.

5. What is the proposed dose of SC Repronex™? How is the dose determined?

The starting dose is SC 75 or 150 IU menotropins daily for 5 days to patients receiving leuprolide or other gonadotropin-releasing hormone (GnRH) agonists. After 5 days, the dose should be individually adjusted (based on clinical findings, ultrasonographic results, and serum estradiol concentrations) to a range of 75 to 450 IU daily for up to 7 days (total dosing up to 12 days) followed by 5000 to 10000 U hCG 1 day after the last dose of SC Repronex™.

The SC Repronex™ dose is based on the IM Repronex™ dose. A separate dose finding study is not conducted for this NDA. Since menotropins dosing is individualized, its clinical use is inclusive of dose finding.

6. What are the bioanalytical methods for FSH and LH?

[redacted] method to determine FSH and LH concentrations in biomatrices. These were solid phase and 2-site assays in which 2 monoclonal antibodies were directed against 2 separate antigenic determinants on FSH or LH. Serum samples were initially reacted with immobilized monoclonal antibodies directed against a specific antigenic site on the β subunit of the hormone. Europium-labeled antibodies directed against a specific antigenic site on the α or β subunit were then reacted with the hormone, already bound to the solid phase antibody. After dissociation of the europium ion from the labeled antibody, the amount of fluorescence was measured. The intensity of fluorescence correlates with the amount of FSH or LH. The FSH lower limit of quantitation (LLOQ) for these assays is around 0.05 mIU/mL with an intra- and inter-assay variation of <5%. The LH LLOQ for these assays is around 0.05 mIU/mL with an intra- and inter-assay variation of <8%. LH has higher cross-reactivity with hCG than FSH does.

Validated commercial kits are available for FSH and LH determination. The bioanalytical standards for FSH and LH were calibrated against the World Health Organization 2nd International Reference Preparation of HMG.

7. What is the clinical pharmacokinetics (PK) of menotropins?

Absorption

Because of their polypeptide nature, FSH and LH are degraded upon oral administration before absorption. The geometric mean absolute bioavailability of FSH upon IM 150 IU menotropins (Humegon™) is 76%. Absolute bioavailability information for LH is not available in the literature.

Distribution

No information is available on plasma protein binding and organ distribution for FSH and LH.

Metabolism

Both kidney and liver clear FSH. Exact metabolic fate of menotropins has not been characterized. Measurement of FSH and LH metabolic rate is extremely difficult because of the continuous secretion of endogenous FSH and LH.

Excretion

Following single dose IM menotropins, approximately 8% of the dose are excreted unchanged in the urine. Blood concentrations of endogenous FSH and LH decline in a biphasic manner. The FSH and LH half-lives in the initial phase are about 4 hours and 20 minutes, respectively. The FSH and LH half-lives in the terminal phase are about 70 and 4 hours, respectively.

Pharmacokinetic/Pharmacodynamic (PK/PD) Relationships

The dose range between no-effect and follicular hyperstimulation is extremely narrow. No evidence of any correlation exists between plasma menotropins concentrations and its clinical effects. Therefore, menotropins dose needs to be individualized per clinical responses.

Special Populations

Menotropins are not used in the pediatric and geriatric populations. Effect of gender, renal and hepatic insufficiencies on the PK of menotropins have not been reported.

Drug Interactions

No clinically significant drug-drug interactions have been reported for menotropins.

8. What are the formulations used in the clinical studies for NDA 21-047?

Meno 96/02/NL (clinical pharmacology and biopharmaceutics study) administered Menogon®. FPI REP 97-01 and FPI REP 97-02 (clinical safety and efficacy studies) administered the to-be-marketed SC Repronex™ formulation. FPI REP 97-01 is also a clinical pharmacology and biopharmaceutics study. All 3 studies administered SC and IM menotropins.

9. What is the relative bioavailability of SC versus IM menotropins?

Conflicting relative bioavailability results of SC to IM menotropins are observed. Briefly, the Meno 96/02/NL and Dobbs et al. (*Fertil Steril* 62:978 1994) studies follow:

Meno 96/02/NL is a 2-period crossover PK study on single dose SC versus IM of 300 IU Menogon® in 16 healthy female subjects (25 ± 4 years old; mean ± SD). Endogenous gonadotropins were suppressed via daily oral administration of ethinyl oestradiol and lynestrenol. Serial serum FSH concentrations were determined via double-antibody RIA. No serum LH concentrations were determined. The FSH PK follows:

Parameter (unit)	Treatment	Geometric Mean	Point Estimate of Ratio (90% Confidence Interval)
C_{max} (mIU/mL)	SC	5.62	135
	IM	4.15	(120 - 153)
AUC_{0-240h} (mIU.h/mL)	SC	370.1	122
	IM	302.9	(116 - 128)
$AUC_{0-\infty}$ (mIU.h/mL)	SC	385.2	120
	IM	320.1	(115 - 126)
t_{max} (h)*	SC	12	NA
	IM	18	NA

*t_{max} is reported as geometric median
NA is not analyzed

Per 90% confidence interval of the ratio of the FSH C_{max} and $AUC_{0-\infty}$, SC and IM Menogon® are not bioequivalent. FSH C_{max} and AUC_{0-240h} are 35 and 22% higher, respectively, upon SC than those upon IM. Mean serum FSH concentrations-time profiles are in Attachment I.

Dobbs et al. administered single dose SC versus IM 450 IU menotropins (Pergonal®) in a crossover study to 7 women (31.1 ± 0.9 years old; mean ± SD) undergoing ovarian suppression with SC leuprolide acetate. Serial serum FSH and LH concentrations were determined via double-antibody RIA. No detectable rises in serum LH concentrations were observed after either SC or IM menotropins. The FSH PK follows:

Parameter (unit)	Treatment	Median
C_{max} (mIU/mL)	SC	14.6
	IM	17.8
AUC (mIU.h/mL)	SC	760 (558 – 1215)†
	IM	1041 (602 – 1246)†
t_{max} (h)	SC	15.8
	IM	8

†numbers in brackets are ranges

FSH C_{max} and AUC are 18 and 27% higher, respectively, upon IM than those upon SC. Individual serum FSH concentrations-time profiles are in Attachment I.
These observations are opposite to those of study Meno 96/02/NL, which may be due to:

- Different SC and IM injection sites. Study Meno 96/02/NL administered SC Repronex™ to the abdomen under the umbilicus and Dobbs et al. administered SC Pergonal® to the left gluteus maximus region. Study Meno 96/02/NL administered IM Repronex™ to the upper lateral quadrant and Dobbs et al. administered IM Pergonal® to the left gluteus maximus muscle. SC insulin to the abdominal area is known to be better absorbed than SC insulin to the thigh and deltoid area.
- Body weight difference of subjects between studies. Subjects weigh 65.0 ± 6.1 kg (54.2 – 72.9 kg) in study Meno 96/02/NL. Subjects are obese and weigh 81.3 ± 8.4 kg in Dobbs et al.'s study. The difference of subjects' subcutaneous fat between studies may affect the PK of SC FSH.

These observations highlight the importance of stipulating the site of SC Repronex™ in the labeling as the lower abdomen (alternating sides), which was the site of SC Repronex™ in the 2 clinical safety and efficacy studies (FPI REP 97-01 and FPI REP 97-02).

10. How did the sponsor conduct the multiple dose Repronex™ clinical pharmacology study?
In study FPI REP 97-01, oligoovulatory infertile patients received either 150 IU SC or IM Repronex™ or IM Pergonal® daily for 5 days. Menotropins dose was individualized afterwards up to 450 IU daily for 7 days. Endogenous FSH and LH were suppressed via daily leuprolide injection before and during the SC and IM menotropins. 10000 U IM hCG was administered to each subject at the end of each treatment. Serial blood samples were collected after the 1st and 6th doses. Serum FSH and LH concentrations were determined via double-antibody chemiluminescent sandwich immunoassays. Initially, patients received 450 IU menotropins for the 1st day and followed with 225 IU menotropins daily for 4 days. This higher dosing scheme resulted in follicular overstimulation. The protocol was then amended to start 150 IU menotropins daily instead. Sponsor used the population approach to analyze the PK data. Hence, Pharmacometrics consult was requested.

11. Are Repronex™ doses linear (SC and IM 150 to 450 IU/day)?
Per Pharmacometrics/Dr. Fossler's analysis (Attachment II), FSH PK appears to be linear up to 450 IU menotropins. Although only 1 subject per SC and IM Repronex™ treatment groups received the 450 IU dose, FSH upon both SC and IM Repronex™ do not appear to depart grossly from linearity.

Serum LH concentrations upon multiple dose SC or IM Repronex™ are low and variable. No recognizable trend in the increase in serum LH concentrations from SC or IM 150 to 450 IU Repronex™ doses was observed. After the 6th dose of SC or IM 150 IU/day Repronex™, the range of baseline-corrected serum LH concentrations is 0 to 3.2 mIU/mL for both routes of administration. These observations are consistent with Dobbs et al's observations. Therefore, LH dose linearity upon SC and IM Repronex™ cannot be assessed.

Lack of LH versus FSH PK data upon multiple dose SC Repronex™ should not cause clinical concern, since the contribution of LH to induction of ovulation (chiefly achieved via hCG administration) is minimal.

12. Does Repronex™ accumulate upon multiple dose SC or IM?
Per Pharmacometrics/Dr. Fossler's analysis (Attachment II), the mean accumulation factors for FSH upon 6 doses of SC or IM 150 to 450 IU/day Repronex™ are 1.6 and 1.4, respectively. Upon 6 doses of SC or IM 150 IU/day Repronex™, the observed serum FSH concentrations range from 1.7 to 15.9 mIU/mL and 0.5 to 10.1 mIU/mL, respectively.

Repeated IM 150 IU/day menotropins (Humegon™) to 7 women on 8 consecutive days lead to gradual accumulation of FSH concentrations which plateau in 3 to 4 days. These observations are consistent with that of study FPI REP 97-01.

However, these observations also indicate the importance of careful and frequent monitoring of clinical findings, ultrasonographic visualizations, and serum/urine estradiol concentrations for patients to minimize the risk of OHHS (Question 4 above).

LH dose accumulation upon multiple dose SC and IM Repronex™ cannot be assessed per reasons indicated in Question 11 previously.

13. What are the covariates for Repronex™ PK?
Dr. Fossler's analysis (Attachment II) shows that no covariates appear to associate with FSH PK upon single and multiple SC or IM Repronex™ (based on 2 studies with small number of subjects). Since serum LH concentrations upon multiple dose SC and IM Repronex™ are low and variable, no model can be fitted for the LH covariate analysis.

14. What are the proposed dissolution methods and specifications for SC Repronex™?
All components of Repronex™ are water soluble. Repronex™ is a parenteral product and is reconstituted with normal saline before SC. Hence, no dissolution specification and method were needed.

15. How does the chemistry of FSH affect its PK/PD?
Serum estradiol and possibly GnRH influence the amount of sialic acid in FSH. The higher the serum estradiol concentrations the less glycosylated the FSH, which results in shorter elimination half-life but with greater receptor affinity. Commercial human menopausal urinary FSH contains more sialic acid and consequently has a longer elimination half-life.

Comments

1. The SC injection site of menotropins appears to affect FSH PK (Question 9 above). Although no correlation exists between plasma menotropins concentrations and its clinical effects (Question 7 above), the "DOSAGE AND ADMINISTRATION" section of the labeling should still stipulate the SC injection site of Repronex™ as the lower abdomen (alternating sides), which

was used in the 2 clinical safety and efficacy studies. This SC injection site stipulation will aid patients to self-administer SC Repronex™.

2. Pharmacometrics communicated the findings of the population PK review (Attachment II) to the sponsor via a teleconference on July 6, 1999. Namely, the FSH covariate analyses are likely spurious and should not be used for labeling (Question 13 above). Rather, the labeling should reflect the lack of covariates' effect on FSH PK upon single and multiple dose of SC or IM menotropins, which is based on a small number of subjects. The sponsor concurred to these findings.
3. The sponsor should consider the following "Suggested Statements for the CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION Sections of the Labeling."

Comments NOT to be conveyed to the Sponsor

Sponsor's Proposed Labeling
See Attachment IV.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 21-047 dated October 26, 1998. OCPB/DPEII finds that the submitted information supports the "Human Pharmacokinetic and Bioavailability" section of NDA 21-047. Comments 1 to 3 above should be conveyed to the sponsor.

Suggested statements for the CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION Sections of the Labeling

CLINICAL PHARMACOLOGY

/S/ August 11, 1999

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

/S/ 8/11/99

Michael J. Fossler, Pharm.D., Ph.D.
OCPB/DPEII

An Optional Inter-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-047 was conducted on July 23, 1999. The participants included S. Slaughter, D. Chatterjee, G. Singh, D. Hare, R. Hassall, A. Selen, D. Moore, S. Madani, A. Parekh, M. Chen, S. Huang, S. Haidar, R. Mozersky, and J. Lau.

FT signed by Ameeta Parekh, Ph.D., Team Leader /S/ 8/11/1999

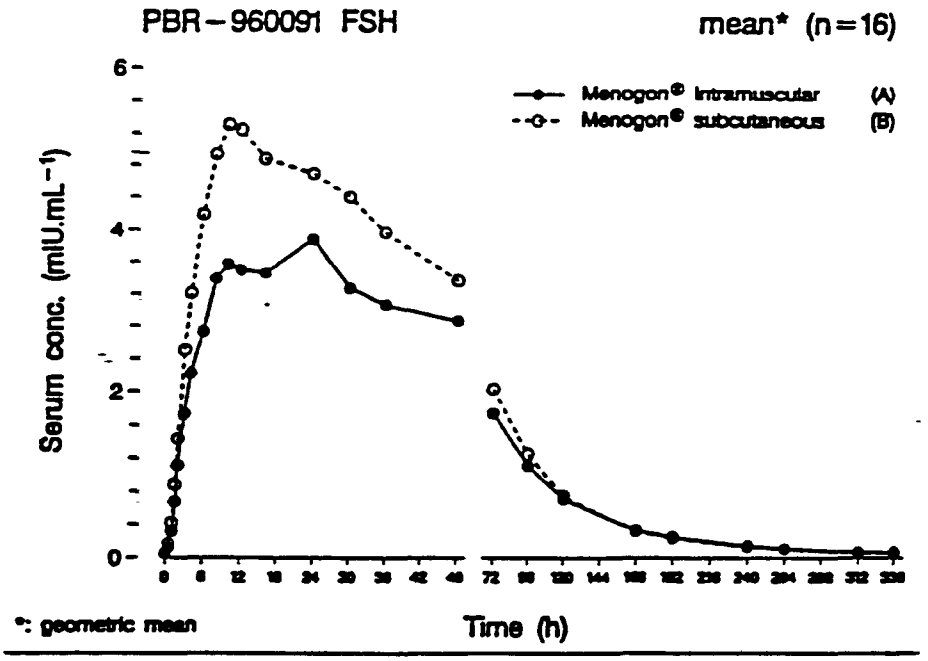
cc: NDA 21-047, HFD-870 (M. Chen, A. Parekh, J. Lau, M. Fossler), HFD-580 (R. Bennett, D. Moore), CDR (B. Murphy for Drugs)

ATTACHMENT 1

4.3.3 Pharmacokinetic results

The mean FSH serum concentration-time curves are given in Figure 1. When comparing these curves it becomes apparent that, on average, subcutaneous Menogon® administration leads to higher FSH serum levels than intramuscular administration.
Subcutaneously administered Menogon® appears to result in faster absorption when compared with intramuscular administration, indicated by the steeper initial increase of FSH serum levels.
The individual serum concentration-time curves of FSH are given in given in Figure 2 and in section 8.2. These curves suggest that intramuscular administration is associated with less variation between the subjects than subcutaneous administration.

Figure 1. Mean serum concentration-time curves of FSH as observed with multiple dose, once- daily oral administration of Ovanon® for seven weeks with single dose administration of Menogon® (300 IU LH and 300 IU FSH) in week 4 and 6 via:
A = intramuscular injection
B = subcutaneous injection



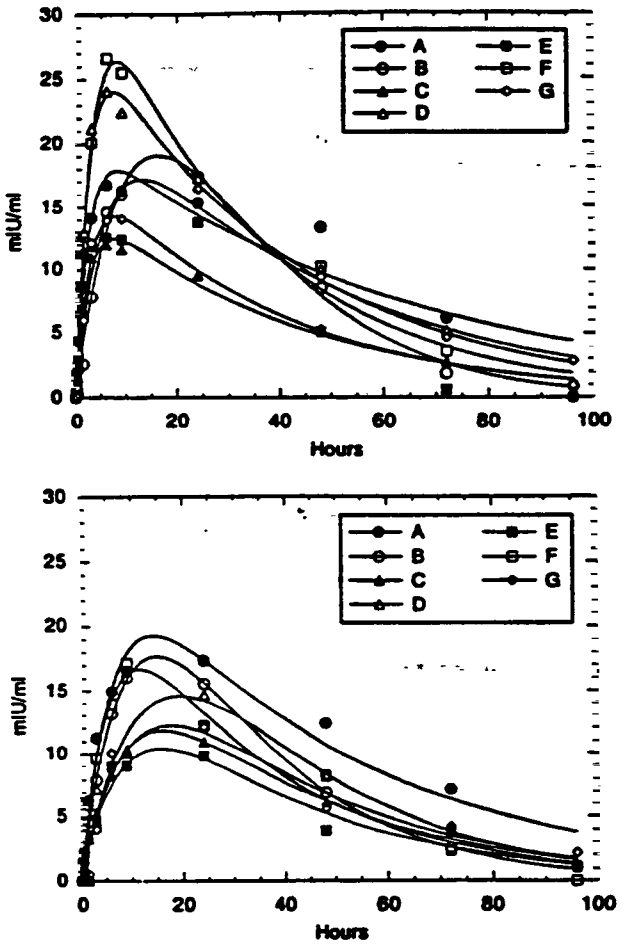


Figure 2 The individual serum FSH concentration levels, together with the first-order curves generated for our seven subjects using IM (top) and SC injection sites (bottom).

age person. Our subjects must be considered as obese by body mass index and mean gross weight. This might have resulted in a larger volume of distribution for the administered menotropins and thus the development of a lower serum concentration than would be expected in a lean population. However, because our comparisons between SC and IM administration are made within individual subjects, the differences that we demonstrated would also be expected in lean women.

We were not able to detect a rise in serum LH after either SC or IM administration of hMG. A combination of several factors probably accounts for this result. The half-life of LH in serum is considerably shorter than that for FSH, which makes it likely that, as a result of degradation, the amount of immunogenic hormone actually absorbed from the depot site was less for LH than for FSH. Furthermore, the actual quantities of immunogenic LH used for injection were less than those of FSH. The commercially available hMG used in this study contains equal amounts of bioassayable FSH and LH. However, when we performed our standard immunoassays for these pituitary gonadotropins on spiked serum samples, we found that the amount of assayable LH per vial was substantially less than the amount of FSH (23.4 ± 8.5 versus 66.0 ± 1.4 IU). Therefore, a considerably larger dose of the commercial hMG product most likely would be necessary to detect and quantify a rise in serum LH after IM or SC administration. The information we gathered does, however, underscore current uncertainties regarding the contribution that exogenous LH makes to ovarian stimulation during hMG-induced follicular development (13).

Chemical alterations of parenterally administered agents can take place at injection sites before absorption into the general circulation. For FSH, such changes could take the form of nicks in the peptide chains or removal of sugars from the carbohydrate side chains. Either type of reaction might affect the rate of clearance of these molecules once they had been absorbed into the circulation or their biological effects at target sites (13). In addition, more profound degradative reactions could occur, resulting in products unrecognizable as FSH by immunoassay. We found that unlike the absorption rate constants, elimination rate constants for immunoreactive FSH coming from the two injection sites did not differ substantially. This result suggests that although the hormone may have different residence times, any minor structural modifications that occurred during depot residence were of the same form and degree. The possibility that outright degradation of FSH occurs at either injection site cannot be determined with the protocol used in this study because it does not allow for the measurement of total hormone uptake into the circulation.

During our work with the volunteer subjects of this project, it became evident that it was often necessary to insert the needle considerably further than 1.5 inches (38 mm) to reach tissue that would provide an action potential. Undoubtedly, the relative obesity of our subject cohort contributed to the depth of needle placement required to reach muscle. In retrospect it would have been of interest to measure this depth. Nevertheless, this observation re-enforces our belief that, in many instances, drugs administered as IM injections do not reach their intended target tissue.

Our study demonstrates that peak levels of FSH

ATTACHMENT II

Pharmacometrics Consult

NDA:	21-047
Menotropins for Injection (75 IU FSH + 75 IU LH) (Repronex®)	
Original Submission Date:	3 February 1999
Sponsor:	Ferring Pharmaceuticals
Type of Submission:	Population PK analysis
Consult received by Pharmacometrics:	21 April 1999
Primary Reviewer:	Johnny Lau
Medical Division:	HFD-580 (Reproductive/Urologic)
Reviewer:	Michael J. Fossler
Consultant:	Gur Jai Pal Singh

Submission

Repronex, (75 IU FSH and 75 IU LH) is approved for IM injection for induction of ovulation, in vitro fertilization, and spermatogenesis. In the present submission, the firm seeks approval for subcutaneous administration for the same indications. Two clinical pharmacology studies were performed to support the sc indication (detailed below).

At the request of the primary reviewer, Pharmacometrics was asked to review the studies and answer the following questions:

- Describe the pharmacokinetics of Repronex after a 450 IU dose
- Comment on the reliability of the analyses.
- Describe the PK of Repronex sc and IM across the dosing range (150, 300 IU)

Study Design

The two studies are summarized in Table 1 below:

Table 1: Summary of submitted studies.

Study Number/Title	Description
MENO 96/02/NL – A Comparative Pharmacokinetics Study on FSH from a urinary HMG (MENOGON®) Preparation after Intramuscular and Subcutaneous Injection in Healthy Female Volunteers	Randomized, two treatment, single-dose crossover study in 16 healthy female volunteers. Each volunteer was given a single IM or SC dose of Menogon separated by 2 weeks. The formulation given was the European formulation (MENOGON®)which differs from the U.S. in the amount of lactose in the formulation. Only FSH was measured in this study
FPI REP 97-01 – A Randomized, Open-Label, Parallel Group, Multi-Center Pharmacokinetic/Pharmacodynamic Study in Anovulatory and Oligo-ovulatory Infertile Female Patients Comparing Repronex SC, Repronex IM and Pergonal IM for Ovulation Induction	Open-Label, randomized, parallel group, multi-center study comparing one cycle of treatment with Repronex SC or IM , or Pergonal IM. Each patient was down-regulated with daily Leuprolide injections until serum estradiol levels were < 30 pg/ml. The patients were then started on the gonadotropins (either sc or IM). Initially, the dose was 450 IU on day 1 followed by 225 IU qd x 4 days. This dose caused over-stimulation, so the protocol was amended to give a dose of 150 IU daily for 5 days.

	followed by individualized dosing of up to 450 IU for up to 12 days. 48 women participated in the PK portion of the study. Samples for FSH and LH analysis were taken on Days 1 and 5 post-dose at 0, 1, 2, 4, 6, 8, 10, 12 and 24 hours.

Pharmacokinetics Analysis Methods

The program P-Pharm® was used to analyze the data from both studies. Dr. Gur Jai Pal Singh of OGD was asked to assist [redacted] with the analysis because of his expertise in the use of P-Pharm. For Study MENO/96/02/NL, the data were modeled in three steps:1) IM administration, 2) SC administration, and 3) Simultaneous fit with both IM and SC data. For Study FPI REP 97-01, the data were separately analyzed as follows: 1) Pergonal IM, 2) Repronex IM, 3) Repronex SC.

For both studies, the analysis was similar. Each subject was first fit individually. Then, a population analysis (without covariables) was carried out. Plots were created to examine the effect each covariate had on the PK parameters. Stepwise linear regression was then performed in order to select the covariates which explain a significant amount of the variability in each PK parameter of interest.

The assay of both FSH and LH should be discussed briefly. At the time that this consult was received, the primary reviewer had no data on the validity of either assay. Since then, the firm has provided data which shows that both the FSH and LH assays used for the studies have been validated.

Results

Study 96/02

Table 1 compares the firm's results from the three-step modeling (IM, SC, Both). The parameter estimates for all three analyses are very similar, which is expected, since the study is of crossover design. The absorption of FSH after SC administration appears to be more variable than after IM. This may be due to differences in tissue perfusion., and again is not completely unexpected.

The firm's covariate analysis yields some contradictory results. For the IM only analysis, volume of distribution appears to be strongly (and positively) associated with age. However, for the SC-only analysis, age appears to have a negative effect on Vd. For the combined analysis, no covariate affects Vd, but clearance appears to be negatively associated with age.

Table 1: Mean FSH Pharmacokinetics parameters from Study 96/02 after IM, SC administration of a gonadotropin preparation (MENOGON®) to 16 healthy female volunteers. Values in the top half of the table are mean ± SD (CV%). The bottom half of the table shows the covariates which were found to have a significant effect in explaining variability in any one of the parameters. na – not applicable, ns – not significant.

Parameter	IM Data Only	SC Data Only	IM, SC Data
ka	0.1174±0.0250 (21.3%)	0.1281±0.0539 (42.05%)	0.1569±0.0339 (21.57%)
CL/F	0.9408±0.0651 (6.9%)	0.7696±0.1315 (17.08%)	0.8342±0.0684 (8.20%)
V/F	57.68±6.57 (11.4%)	39.37±5.544 (14.08%)	51.73±5.242 (10.13%)
F_{rel}	na	na	1.01±0.16 (15.87%)
Significant Covariate Relationships			
ka	ns	ns	0.05118*TRT +0.0802
CL/F	0.03347*BMI + 0.175	ns	-0.0119*AGE+1.12
V/F	1.8507*AGE +11.99	-1.329*AGE + 72	ns
F_{rel}	na	na	ns

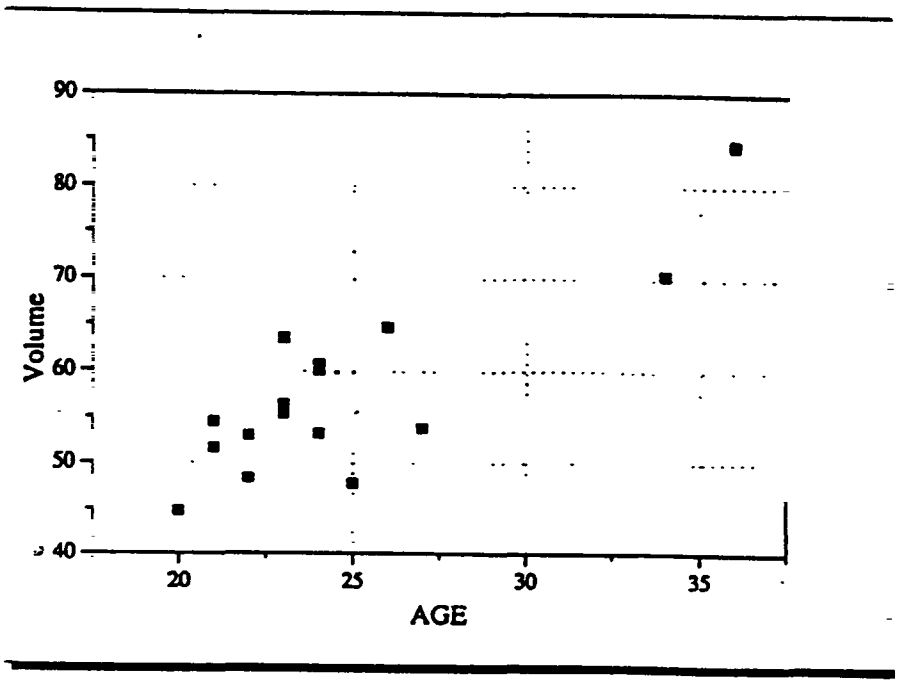
It is difficult to reconcile these contradictory results in a satisfactory way. The firm offered no explanation for the contradictory results. However, the reviewer is of the opinion that the contradictory nature of the relationships is a strong indication that the results are spurious. Other major evidence for this point of view is that the addition of the above covariates to the model did very little to change the AIC of any of the baseline analyses. Table 2 displays the AIC values of the base model (without covariates) followed by the values for the final model. After the addition of covariates to the model, the AIC values barely change, which indicates that the addition of these additional parameters is having no effect on the fit and should not be included in the final model.

Table 2: AIC values for the three analyses at baseline (no covariates) and after the addition of covariates.

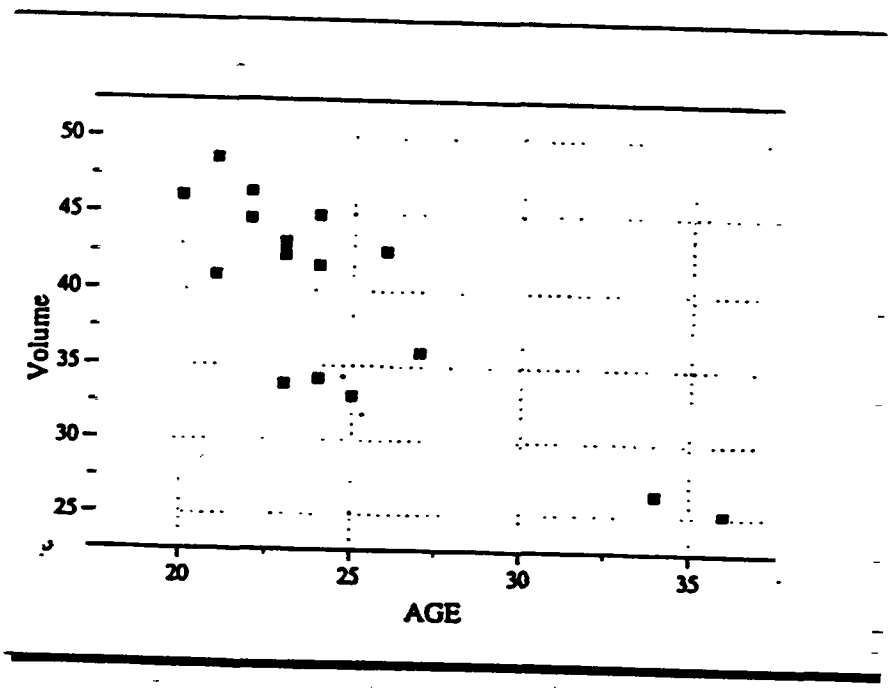
	IM only	SC only	Both
Baseline AIC	-7.107	-7.368	-7.455
Final Model AIC	-7.127	-7.361	-7.459

The other piece of evidence that the covariate results are spurious is provided by an examination of the parameters vs. covariate plots. Three of these are shown in Figure 1a-c. Looking at all three, one can see that the linear relationship of age with Vd or Cl is primarily driven by the two older women included in the study. When these points are removed from consideration, the relationship becomes much less impressive in each case. Figure 2 depicts a plot of Cl as a function of BMI; again, this relationship appears to be driven by two subjects with high BMIs.

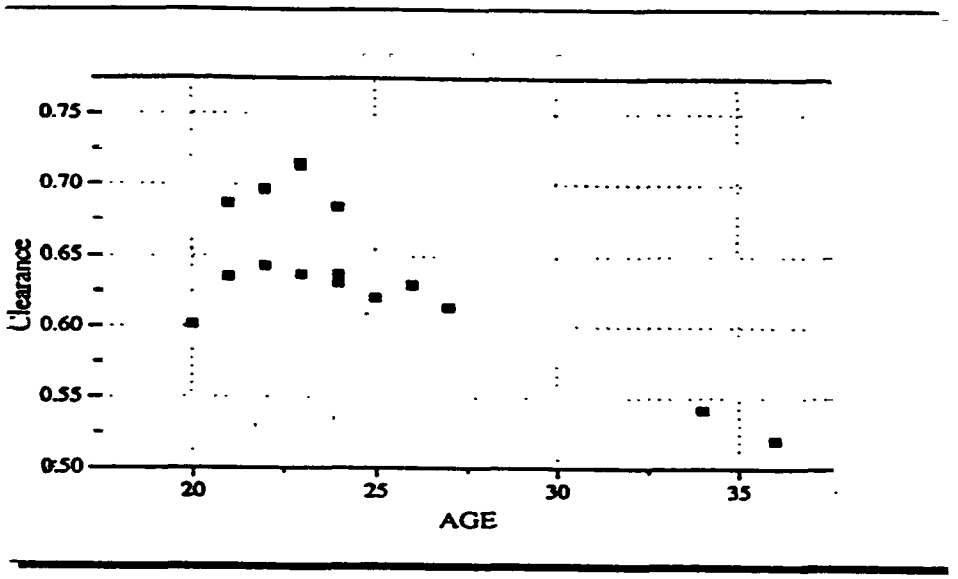
Figure 1a-c: a) Vd vs. Age from IM analysis. b) Vd vs. Age from SC analysis. c) CL vs Age from combined analysis.



(a)

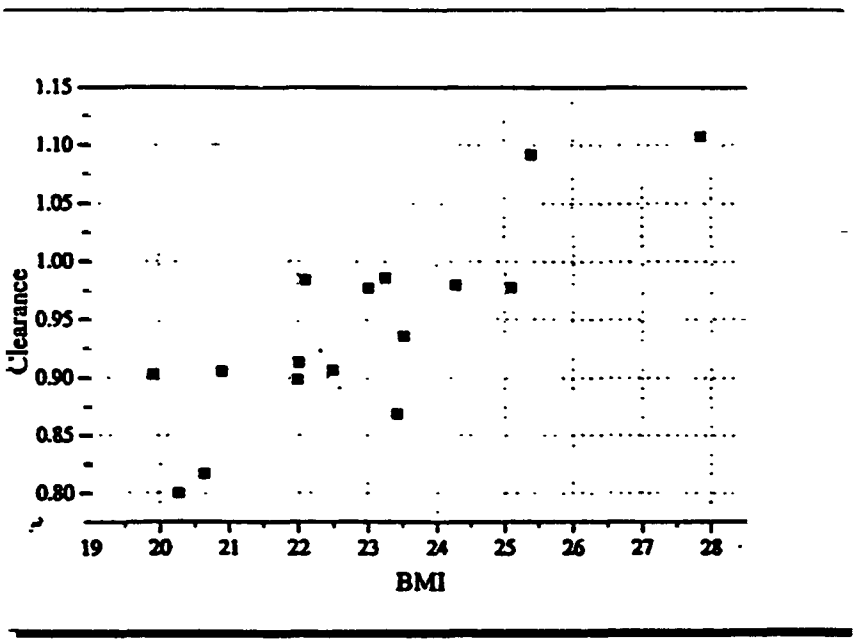


(b)



(c)

Figure 2: Cl vs. BMI from the IM analysis.

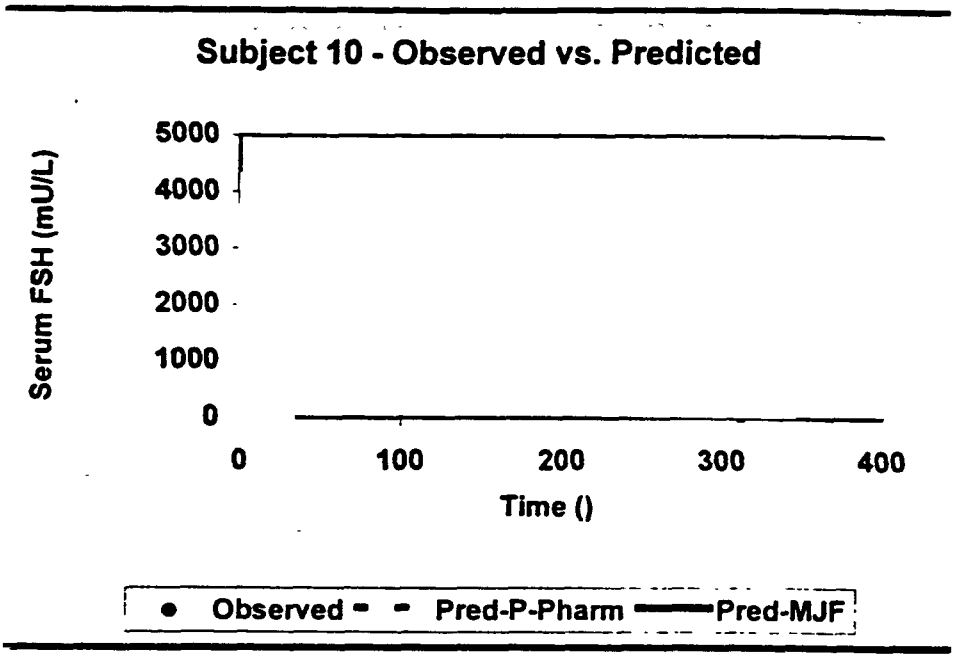


The relationship between treatment (SC or IM injection) and the absorption rate constant is shown in Figure 3. The method of injection does seem to affect ka, although the slope of the line (0.05118, in Table 1) is not large. This indicates that the effect is rather small. This is supported from an examination of the peak concentrations obtained in this study. Mean peak concentrations after SC injection are higher (5784, range 3120-8894) than after IM injection (4188, range 2490-5952); however, there is considerable overlap.

Figure 3: Absorption rate constant (ka) as a function of treatment (1=IM, 2=SC)

Quite apart from the covariate analysis, it appears from examining the observed vs. predicted FSH concentration plots that the PK model does a poor job of fitting the data around Cmax . Figure 4 shows a typical example. The dotted line is the predicted concentrations resulting from the sponsor's analysis The solid line is the predicted concentrations resulting from the reviewer's analysis using WinNonLin. For this patient, the reviewer's fit is considerably better. Since the product used in this study is not the one that is marketed in the U.S., it is unclear whether anything could be gained by re-analyzing these data, but it is indicative of a problem with the firm's analysis. Pharmacometrics feels that this may be in part due to an improper weighting scheme being used for the FSH data. The firm used $1/y^2$, which will favor low concentrations at the expense of high concentrations. No justification for the use of $1/y^2$ was provided. This may explain the bias seen. For the individual fit, and for the analysis of Study 97/01, the reviewer used 1 weighting scheme of $1/y$, which appears to be less biased toward high concentrations.

Figure 4: Observed vs. predicted FSH concentrations for Subject 10 given 300 IU IM. The reviewer's fit to these data is considerably better



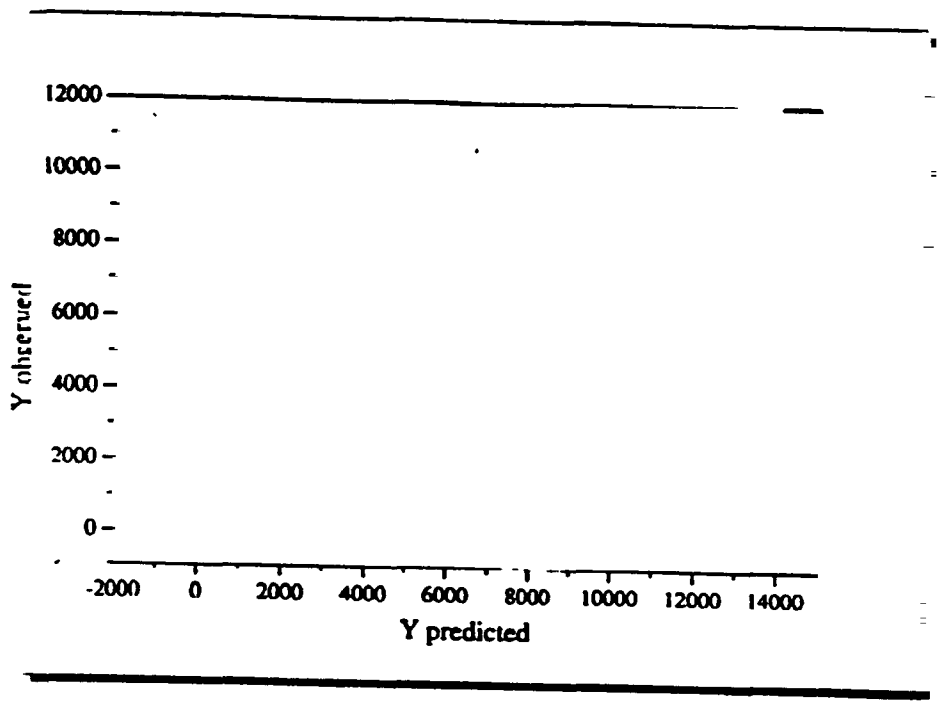
Study 97/01- FSH

The results for the FSH portion of the analysis are shown in Table 3. Although the clearance and volume estimates for the two analyses are similar, the estimates of ka differ quite markedly between the two analyses. Again, the firm used some covariates in the model (age , weight); however, as in the previous study, the addition of these covariates to the model did not significantly change the AIC, so the inclusion of these covariates in the model is unjustified. Figures 5a-b compare the observed vs. predicted plot for the firm's reviewer's analysis. Figure 6a-b depicts observed vs. predicted fits for two subjects . In both figures, the reviewer's fit is considerably better, although there is still some unexplained variability in the data.

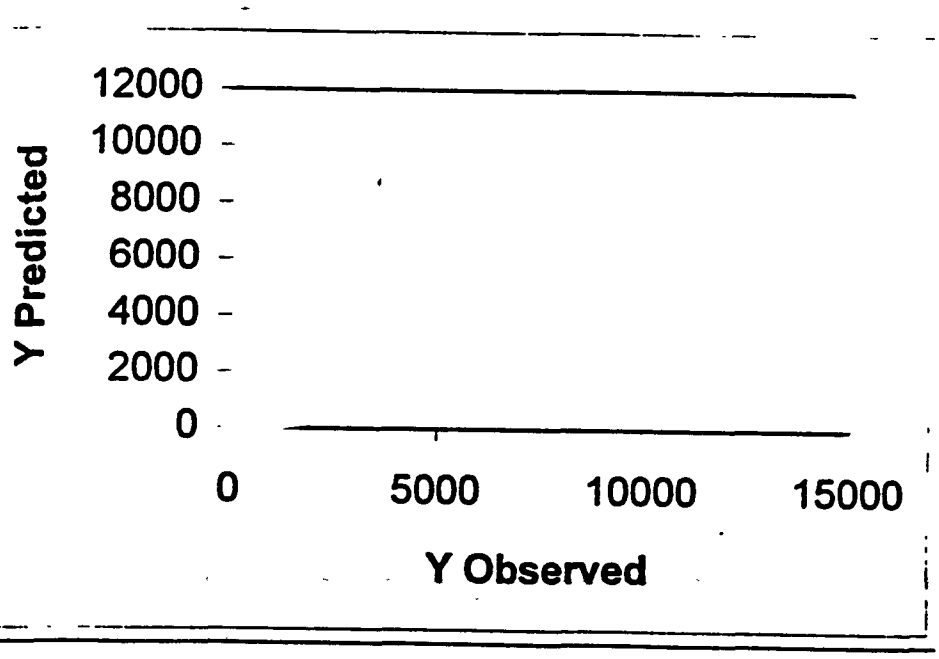
Table 3: Mean PK parameters resulting from firm's analysis and reviewers' analysis. ns: not significant

	Firm's Analysis		Reviewer's Analysis	
Parameter	**Repronex IM**	**Repronex SC**	**Repronex IM**	**Repronex SC**
ka	0.220±0.233 (106%)	0.423±0.424 (100.1%)	0.0638±0.0404 (63.2%)	0.076±0.0351 (46.3%)
CL/F	1.09±0.231 (20.9%)	0.974±0.136 (14.0%)	1.44±0.626 (43.5%)	1.11±0.441 (39.5%)
V/F	20.2± 9.71 (48.1%)	44.4±21.4 (48.2%)	23.5±0.599 (2.54%)	23.09±1.91 (8.26%)
Significant Covariate Relationships				
ka	ns	ns	ns	ns
CL/F	ns	0.008*Wt-0.55	ns	ns
V/F	1.967*Age-35.01	ns	ns	ns

Figure 5a-b: Individual Observed vs. Predicted plots for a) firm's analysis of the Repronex IM data (note that the firm incorrectly plotted the observed concentrations on the y-axis). b) Reviewer's analysis of the Repronex IM data



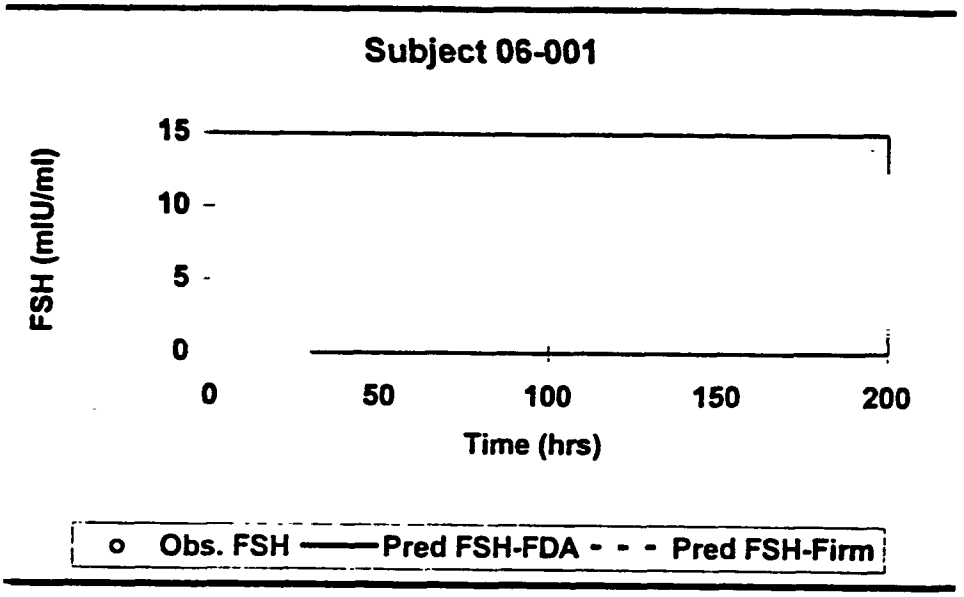
(a)



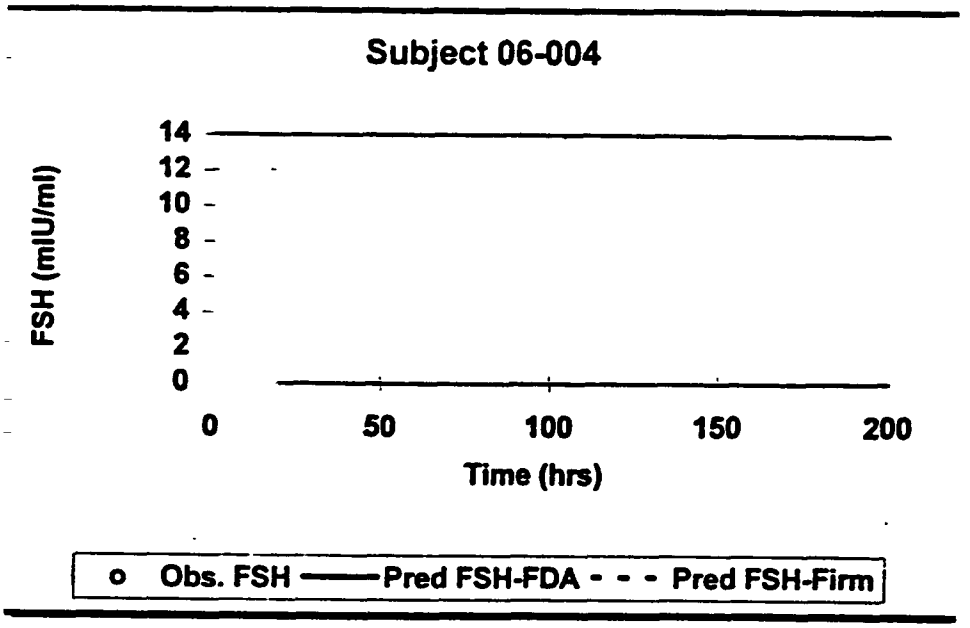
(b)

The straight line in figures 6 a and b between 24 and 120 hour indicates no samples were taken. JF Aug. 10, 19

Figure 6: a) Observed vs. predicted of Subject 06-001, given 450 IU Repronex x1 followed by 225 IU x 5 IM. b) Observed vs. predicted of Subject 06-004, given 450 IU Repronex x1 followed by 225 IU x 5 SC.



(a)



(b)

Although the firm did attempt to fit the LH data, the resulting fits were extremely poor. An attempt was made by the reviewers to re-fit these data; however, major problems were encountered in doing so. As stated by Dr. Singh the major problem appears to be the presence of zero concentrations in the middle of the steady-state profiles. Also, many of the profiles have unusual shapes (Figure 6). It is unclear why this is so. Because of the poor quality of the data, it was felt that no additional resources should be spent in attempting to fit the LH concentrations. Pharmacometrics suggests that the range of steady-state LH concentrations be reported in the labeling.

Reviewer Comments

1) Although only two subjects received doses up to 450 IU, the pharmacokinetics of FSH appear to be linear up to this dose (Figure 6 a,b). At the very least, there does not appear to be any gross departure from linearity. Whether these data are sufficient for a firm conclusion regarding linearity depends on the safety margin of the compound.

2) As stated above, the covariate analyses for FSH are likely spurious and should not be used in labeling. Rather, labeling should reflect the lack of effect of covariates, with the caution that the studies on which this conclusion is based are rather small. The PK parameter estimates resulting from the reviewer's analysis should be incorporated into the labeling, as in Table 3.

3) Pharmacometrics recommends that a teleconference be set up in order to discuss these findings with the firm.

/S/ 6/28/99

Michael J. Fossler, Pharm.D., Ph.D.

Pharmacometrics Consultant
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT reviewed by Raymond Miller, D.Sc. 6/24/99

CC: NDA 21-047(orig., 1 copy), HFD-850(Lesko, Ray Miller), HFD-870(M.Chen, Fossler,),

J. ACCUMULATION CALCULATIONS FOR PATIENT STUDY.

Repronex IM

Subject	CL/F	V/F	kel	t1/2	R
04-001					
04-005					
06-001					
06-005					
06-009					
06-011					
06-015					
06-017					
06-019					
06-024					
09-004					
09-006					
09-007					
09-012					
10-001					
Mean	1.44	23.55	0.06	12.98	1.40
SD	0.63	0.60	0.03	4.43	0.23
Min					
Max					

Repronex SC

Subject	CL/F	V/F	kel	t1/2	R
04-002					
04-006					
06-004					
06-014					
06-018					
06-020					
06-022					
06-025					
06-026					
09-002					
09-003					
09-008					
09-010					
09-013					
09-014					
10-002					
10-004					
Mean	1.12	23.10	0.05	16.82	1.60
SD	0.44	1.91	0.02	7.26	0.41
Min					
Max					

Attachment III

Protocol Number: Meno 96/02/NL

Study Title:

A comparative pharmacokinetic study on FSH from a urinary HMG (Menogon[1]) preparation after intramuscular and subcutaneous injection in healthy female volunteers.

Investigators and Location:

Objectives:

compare FSH PK after IM and SC administration of Menogon® in healthy female volunteers

Study Design:

This was a single dose, open-label, randomized, 2-way crossover PK study with a washout period of at least 2 weeks between drug administration. Sixteen healthy female subjects (16 completed) received orally 50 µg ethinyl oestradiol and 2.5 mg lynestrenol (Ovanon®) daily for 6 weeks. At the beginning of week 4 Ovanon® treatment, subjects received single dose of 300 IU of FSH and 300 IU of LH (Menogon®) via either IM injection to the upper lateral quadrant or SC injection at the abdomen under the umbilicus. At the beginning of week 6 Ovanon® treatment, subjects received the same dose of Menogon® via a route that was not received at the beginning of week 4.

Drug Administration:

1. 75 IU LH and 75 IU FSH (Menogon®), Batch 96225
2. 50 µg ethinyl oestradiol and 2.5 mg lynestrenol (Ovanon®), Batch 070601

Blood Sampling and Bioanalytical Analysis:

Blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96, 120, 168, 192, 240, 264, 312, and 336 hours after each Menogon® injection for the determination of serum FSH concentrations.

Serum FSH concentrations were measured via an immunoassay analyser, Immulite[2].
Linearity: Non-linear. Calibration range was 0.0496 to 170 mIU/mL
Accuracy: 2.5 to 5.3%
Precision: 5.2 to 5.5% CV
LLOQ: 0.0496 mIU/mL

Pharmacokinetic and Statistical Analysis:

Protocol Number: FPI REP 97-01

Study Title:

A randomized, open-label, parallel group, multi-center pharmacokinetic/pharmacodynamic study in anovulatory and oligoovulatory infertile female patients comparing Repronex™ S.C., Repronex™ I.M., and Pergonal® I.M. for ovulation induction.

Investigators and Location:

Benjamin Gocial, M.D., Philadelphia, PA, John Queenan, M.D., Mt. Pleasanr, SC, Billy Kutteh, Memphis, TN, Edward Moore, M.D., Columbia, SC, John Nichols, M.D., Greenville, SC, Milton McNichol, M.D., Houston, TX, Bill Schlaff, M.D., Denver, CO, Eric Knochenhauer, M.D., Birmingham, AL, David Walmer, M.D., Durham, NC, Jack Crain, M.D., Charlotte, NC,

Objectives:

Single dose and multiple doses PK of FSH and LH upon administration of menotropins

Study Design:

This was a multiple-dose, open-label, randomized, 2-way parallel efficacy study in anovulatory and oligoovulatory infertile female subjects. Each subject received leuprolide injections (up to 20 days) commencing on day 2 of menses (spontaneous or by progesterone induction) until serum estradiol concentrations were ≤ 30 pg/mL. Within 3 days of serum estradiol concentrations were ≤ 30 pg/mL, subjects received 150 IU of FSH and 150 IU of LH (Repronex™) via either IM or SC injection or 150 IU of FSH and 150 IU of LH (Pergonal®) as IM injection daily for 5 days and then dosing to a maximum of 450 IU FSH and 450 IU LH daily for a total treatment duration of less than 12 days. Each subject received 10,000 USP units IM hCG following the last dose of gonadotropin.

Drug Administration:

1. Leuprolide injection qd ; leuprolide dose, site of injection, and Batch were not provided
2. Repronex™ SC and IM 150 - 450 IU qd, Batch 506 421-447/507 421-610
3. Pergonal® IM 150 - 450 IU qd, Batch 03319077-B
4. hCG injection 10000 U IM; Batch was not provided.

Blood Sampling and Bioanalytical Analysis:

Day 1 and day 5 extensive sampling for the determination of serum FSH and LH concentrations via

Pharmacokinetic and Statistical Analysis:

PPHARM and SAS softwares were used to assess population pharmacokinetics of FSH and LH.

Results and Conclusion:

See Pharmacometrics/Dr. Fossler's review (Attachment II).