CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-582

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SEP 29 1997

Clinical Pharmacology and Biopharmaceutics Review

Amendment to Review

NDA:	20-582
Compound:	Follitropin Beta (Org 32489) for Injection (75 IU/vial and 150 IU/vial)
Sponsor:	Organon, Inc.
Type of Review:	Amendment to Clinical Pharmacology and Biopharmaceutics Review dated March 27, 1997 (submitted January 9, 1997).
Reviewer:	K. Gary Barnette, Ph.D.

SYNOPSIS/BACKGROUND

NDA 20-582 (Follitropin Beta for injection), recombinant follicle stimulating hormone (r-FSH) was submitted January 9, 1996. The proposed indications are the development of multiple follicles in ovulatory patients seeking assisted reproduction and induction of ovulation and pregnancy in the anovulatory infertile patient with functional infertility.

Follitropin (r-FSH) is intended for subcutaneous or intramuscular injection. The recommended starting dose for assisted reproduction therapy is 150 to 225 IU/day for at least 4 days followed by individual dose adjustment based on ovarian response. A reported maintenance dose range of 75 to 600 IU/day was studied in the well controlled clinical trials (not submitted to the Division of Pharmaceutical Evaluation II). The recommended starting dose for ovulation induction in anovulatory infertile patients with functional infertility is 75 IU/day for at least 7 days. If no ovarian response, the dose will be gradually increased until follicular growth and/or serum estradiol levels indicate adequate response. The recommended dosing range for this indication is 75 to 300 IU/day. It should be noted that reconstitution of up to 4 vials of either the to-be-marketed formulations of Follitropin are 75 IU/vial and 150 IU/vial are to be reconstituted in a total of 1 ml NaCl (0.45%).

The submissions to NDA 20-582 (1/9/96, original NDA and 6/21/96, amendment) were reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). On December 12, 1996, OCPB/DPE II recommended the approval of the 75 IU vial of Follitropin, however, the 150 IU vial was not accepted and the following recommendation was made;

> "Since the proposed to-be-marketed 150 IU/vial formulation was not used in any of the clinical or pharmacokinetic trials, based on clinical pharmacology and biopharmaceutic regulations, it is the recommendation of OCPB/DPE II that approval of this formulation strength be withheld pending the conduct, submission and review of a proper *in vivo* bioequivalence study comparing the 75 IU/vial and 150 IU/vial formulation strengths. The proposed protocol for this recommended study should be submitted to the Agency for review prior to initiation."

In a teleconference between the Agency and Organon on March 25, 1997, it was learned that up tc or vials of Follitropin can be dissolved in ml diluent. In the pivotal clinical trials submitted to NDA 20-582 on January 9, 1996 when multiple vials (75 IU/vial) of Follitropin were needed to achieve the desired dose, the following procedure was used;

Therefore, the total volume of injection was ml.

Additionally, Follitropin is labeled to indicate the aforementioned dissolution procedure and that up to vials may dissolved in ml diluent.

On January 9, 1997, Organon Inc. submitted an amendment to NDA 20-582 to address Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) concerns about the 150 IU vial of Follitropin. The submission contained the study report of a multiple dose, pharmacokinetic study to assess the dose proportionality of 75, 150 and 225 IU doses of Follitropin (Study Number 37624), in which each dose was reconstituted in 1 ml of solvent and injected subcutaneously. Therefore, this report also addressed the effect of varying the concentration of injection from 75 IU r-FSH/ml to 225 IU/ml.

In the review of this submission by OCPB/DPEII, dated March 27, 1997 the following recommendation was made;

> "It is the opinion of OCPB/DPEII that the sponsor has provided sufficient information to obtain approval for the 75 and 150 IU/vials of Follitropin for the indications of development of multiple follicles in ovulatory patients seeking assisted reproduction and induction of ovulation and pregnancy in the anovulatory infertile patient with functional infertility.
>
> However, it is recommended that a definitive study to assess the bioequivalence of the 75 IU vial and 150 IU vial of Follitropin be conducted. This study can be performed post-approval, providing the Division of Reproductive and Urologic Drug Products (HFD-580) considers the sponsor has provided sufficient efficacy and safety information to support approval of NDA 20-582 for the indications sought herein."

Amended Recommendation:
However, after further review of these data by OCPB/DPEII the following comments and recommendation are made;

1. The concentration of injection has been shown not to significantly effect the pharmacokinetics of Follitropin.
2. Follitropin has been labeled to indicate a constant injection volume (1 ml)
3. Varying the concentrations of excipients has been shown not to significantly effect the pharmacokinetics of Follitropin.

Therefore, it is the opinion of OCPB/DPEII that sufficient information has been provided for the approval of the 150 IU vial of Follitropin and the previously requested bioequivalence study comparing the pharmacokinetics of the 75 IU and 150 IU vials of Follitropin is not warranted.

K. Gary Barnette, Ph.D.
Office of Clinical Pharmacology and Biopharmceutics
Division Pharmaceutical Evaluation II

RD initialed by John Hunt, Deputy Division Director 9/29/97
FT signed by John Hunt, Deputy Division Director 9/29/97

cc: **NDA 20-582, HFD-580 (Bennet, Pauls), HFD-870 (ML.Chen 13B-17, Dorantes, Barnette), Drug File (CDR, Barbara Murphy).**

Table 1.

Ingredient	75 IU vial
Follitropin	75 IU
Sucrose, NF	25.0 mg
Polysorbate 20, NF	0.1 mg
Sodium Citrate	6.45 mg
HCl (1%) and/or NaOH (1%)	adjust pH
Water, USP	Trace

The proposed to-be-marketed formulation will be reconstituted in 1 ml NaCl (0.45%) per vial. However, in this study each dose (1, 2 or 3 x 75 IU vials) was reconstituted in 1 ml total volume.

Blood Collection: Samples for assessment of FSH were taken at 1, 2, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96, 120, 144, 168, 240 and 366 h after the last FSH dose.

Analytical Methodology:

Table 2. FSH Assay Validation

Target Concentration (IU/L)			
Precision intra-assay CV (%)			
Precision Inter-assay CV (%)			
Accuracy (%)			
LLQ (IU/L)			

The specificity of the this particular FSH assay kit was presented in the original NDA submission (1/9/96) and is included in Table 3.

Table 3. Specificity of FSH assay (% cross reactivity)

Hormone	Kit Manufacturer Specification	Analyst Validation
hTSH	%	%
hLH	%	%
hCG	%	%

Results:

The mean pharmacokinetic parameters after subcutaneous (SC) administration of 75, 150 and 225 IU of Follitropin and after intramuscular (IM) administration of 150 IU of Follitropin are included in Table 4. Additionally, the FSH concentration versus time profiles depicting the various doses of Follitropin by the SC route are included in Figure 1, below. The profiles of the 150 IU doses administered by the SC and IM routes are included in Figure 2, below.

Table 4. Mean ± SD Pharmacokinetic Parameters

Parameter	75 IU, S.C.	150 IU, S.C.	225 IU, S.C.	150 IU, I.M.
n	12	11	10	12
AUC0-24 (IU*h/L)	89.7 ± 11.9	117.7 ± 22.9	292.9 ± 38.8	160.0 ± 24.2
Cmax (IU/L)	4.30 ± 0.60	8.51 ± 1.16	13.92 ± 1.81	7.77 ± 1.09
Css, min (IU/L)	3.34 ± 0.37	6.57 ± 0.71	10.50 ± 1.68	6.09 ± 0.84
tmax (h)	8.4 ± 2.8	7.5 ± 3.4	8.2 ± 3.9	5.3 ± 3.0
t½ (h)	36.2 ± 5.3	34.8 ± 4.6	35.2 ± 2.9	37.1 ± 4.6
Cl/kg (L/h/kg)	0.014 ± 0.002	0.014 ± 0.002	0.014 ± 0.002	0.016 ± 0.002

Figure 1. Mean FSH Pharmacokinetic Profiles after SC Administration, Dose Proportionality

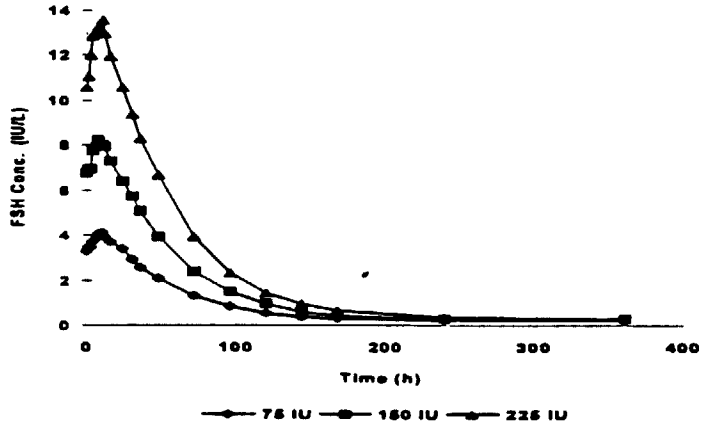
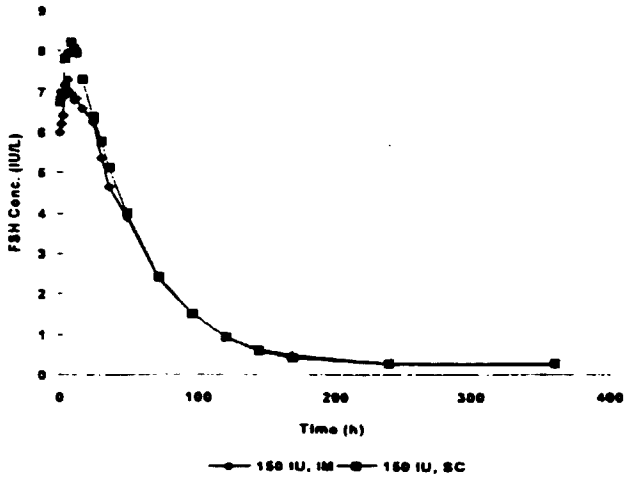


Figure 2. Mean FSH Pharmacokinetic Profile, Subcutaneous versus Intramuscular Administrations



Statistics:
The statistical analysis (90% CI) to assess the dose proportionality of 75 to 225 IU doses of Follitropin are included in Tables 5 and 6.

Table 5. Statistical Comparison of Dose Normalized Log-Transformed AUC

Test v Ref.	Point estimate (Ratio test/reference)	90% CI
75 IU sc v 150 IU sc	0.966	88.5 to 105.4
225 IU sc v 150 IU sc	0.980	89.4 to 107.4
75 IU sc v 225 IU sc	0.985	90.1 to 107.8
150 IU sc v 150 IU im	0.903	82.7 to 98.5

Table 6. Statistical Comparison of Dose Normalized Log-Transformed Cmax

Test v Ref.	Point estimate (Ratio test/reference)	90% CI
75 IU sc v 150 IU sc	1.009	91.8 to 110.9
225 IU sc v 150 IU sc	1.092	98.9 to 120.5
75 IU sc v 225 IU sc	0.925	83.9 to 101.9
150 IU sc v 150 IU im	1.096	99.7 to 120.5

Sponsor's Conclusions:

1. Dose proportionality was observed over the dosing range of IU/day administered subcutaneously.

2. Bioequivalence was observed between a dose of 150 IU given subcutaneously and intramuscularly.

Reviewer Comment:
Since each of the doses (75, 150 and 225 IU) was reconstituted in 1 ml NaCl (0.45%) and dose proportionality was observed, it is concluded that the concentration of injection does not affect the pharmacokinetics (absorption) of Follitropin over a concentration range of IU/ml.

ADDITIONAL INFORMATION

The pharmacokinetic dose proportionality of Follitropin was assessed in a multiple rising dose study (Study 37607) over a dosing range of 75 to 225 IU/day administered by intramuscular injection (previously reviewed by OCPB/DPEII, review dated 12/12/96). This study was conducted in pituitary suppressed (Lyndiol®) healthy females. The mean FSH blood levels from the three doses are depicted in Figure 3, the pharmacokinetic parameters in Table 7 and comparative analysis to assess the proportionality in Table 8.

Figure 3.

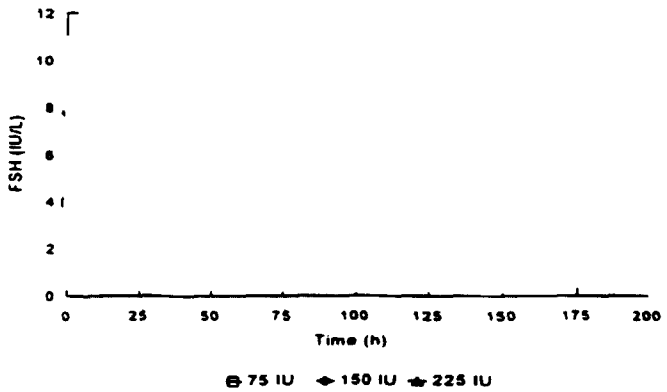


Table 7. Pharmacokinetic Parameters

Study #	Dose	n	AUC0-24 (IU*h/ml)	Cmax (IU/ml)	Tmax (h)	T½ (h)
37607	75 IU	9	96.70 ± 22.28	4.65 ± 1.49	8.21 ± 4.29	26.8 ± 7.8
	150 IU	7	203.68 ± 49.29	9.46 ± 2.57	10.86 ± 6.31	30.1 ± 6.22
	225 IU	8	242.37 ± 44.12	11.30 ± 1.77	11.25 ± 8.04	28.9 ± 6.5

Table 8. Dose Proportionality Comparative Analysis

	Dose adjusted Values		
	75 IU	150 IU	225 IU
AUC (IU·hr/L)	1.50 ± 0.35	1.58 ± 0.38	1.25 ± 0.23
Cmax (IU/L)	0.072 ± 0.23	0.073 ± 0.020	0.059 ± 0.009

The volume of diluent used in Studies 37601, 37607, and RM-9211 was the to-be-marketed volume, 1 ml/vial. However, the volume used in Studies 37602 and 37614 was 0.5 ml/vial. A between study comparison of the pharmacokinetics of the 75 IU/vial (300 IU total dose) dissolved in 1 ml delivered by IM injection (Study 37601) and the 75 IU/vial (300 IU total dose) dissolved in 0.5 ml also delivered by IM injection (Study 37614) was made by this reviewer. The results of this comparison are outlined in Table 9.

Table 9. Pharmacokinetic Comparison; Both Total Doses = 300 IU, Given by IM Injection

Study #	Diluent Volume/Vial (ml)	Subject Weight (kg)*	n	AUC (IU*h/L)#	Cmax (IU/L)	Tmax (h)
37614	0.5	64 (53-72)	13 ♀ - down regulated with Lyndiol®	445.7 ± 135.7	6.86 ± 2.90	18.15 ± 10.15
37601	1.0	67 (43-85)	8 ♀ - gonadotropin deficient	339 ± 105	4.3 ± 1.7	26.9 ± 5 4

- AUC from Study 37614 = AUC0-312, Study 37601 = AUC 0-∞
* - Subject weight is reported as mean (range).

Reviewer Comments:

1. Dose proportionality was observed between the 75 IU/day and 150 IU/day IM doses. However, the 225 IU/day IM dose is not dose proportional with the other two doses.

2. It should be noted that the vials of Follitropin (75 IU/vial) were each reconstituted in 1 ml NaCl (0.45%). Therefore, doses of 75, 150 and 225 IU would be made in a total volume of 1, 2, and 3 ml, respectively.

3. It is acknowledged that the study populations from Studies 37614 and 37601 are different, normal healthy volunteers, down regulated with Lyndiol® and gonadotropin deficient subjects, respectively. However, the observed differences in AUC, Cmax and Tmax between the two studies could be due to the different diluent volume used in each of the studies.

4. The volume of injection may affect the absorption of Follitropin.

RECOMMENDATION

The amendment to NDA 20-582, submitted on January 9, 1997 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII). It is the opinion of OCPB/DPEII that the sponsor has provided sufficient information to obtain approval for the 75 and 150

IU/vials of Follitropin for the indications of development of multiple follicles in ovulatory patients seeking assisted reproduction and induction of ovulation and pregnancy in the anovulatory infertile patient with functional infertility.

However, it is recommended that a definitive study to assess the bioequivalence of the 75 IU vial and 150 IU vial of Follitropin be conducted. This study can be performed post-approval, providing the Division of Reproductive and Urologic Drug Products (HFD-580) considers the sponsor has provided sufficient efficacy and safety information to support approval of NDA 20-582 for the indications sought herein.

The sponsor is encouraged to submit the protocol for the recommended Phase IV bioequivalence study to OCPB/DPEII for comment, prior to the initiation of the study.

The Recommendation should be communicated to the sponsor as appropriate.

K. Gary Barnette, Ph.D.
Office of Clinical Pharmacology and Biopharmceutics
Division Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader, AD 3/25/97
FT signed by Angelica Dorantes, Ph.D., Team Leader Dorantes 3/26/97

cc: NDA 20-582, HFD-580 (Bennet, Pauls), HFD-870 (ML.Chen 13B-17, Dorantes, Barnette), Drug File (CDR, Barbara Murphy).

MAR 27 1997

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-582

Compound: Follitropin Beta (Org 32489) for Injection (75 IU/vial and 150 IU/vial)

Submission Dates: 1/9/97

Sponsor: Organon, Inc.

Types of Submission: Amendment

Reviewer: K. Gary Barnette, Ph.D.

SYNOPSIS/BACKGROUND

NDA 20-582 (Follitropin Beta for injection), recombinant follicle stimulating hormone (r-FSH) was submitted January 9, 1996 and is intended to support approval for the following indications;

- development of multiple follicles in ovulatory patients seeking assisted reproduction
- induction of ovulation and pregnancy in the anovulatory infertile patient with functional infertility

Follitropin (r-FSH) is intended for subcutaneous or intramuscular injection. The recommended starting dose for assisted reproduction therapy is 150 to 225 IU/day for at least 4 days followed by individual dose adjustment based on ovarian response. A reported maintenance dose range of 75 to 600 IU/day were studied in the well controlled clinical trials (not submitted to the Division of Pharmaceutical Evaluation II). The recommended starting dose for ovulation induction in anovulatory infertile patients with functional infertility is 75 IU/day for at least 7 days. If no ovarian response, the dose will be gradually increased until follicular growth and/or serum estradiol levels indicate adequate response. The recommended dosing range for this indication is 75 to 300 IU/day. The proposed to-be-marketed formulations of Follitropin are 75 IU/vial and 150 IU/vial and are to be reconstituted in 1 ml NaCl (0.45%.

The submissions to NDA 20-582 (1/9/96, original NDA and 6/21/96, amendment) were reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). On December 12, 1996, OCPB/DPE II recommended the approval of the 75 IU vial of Follitropin, however, the 150 IU vial was not accepted and the following recommendation was made;

The request for a BA/BE study comparing the clinically tested 75 IU vial and the 150 IU vial formulations of Follitropin was based on the following regulatory/scientific rationale;

1. 21 CFR 320 (page 196)
   (b)...A drug product's in vivo BA or BE may considered self-evident (FDA shall waive the requirement for in vivo BA or BE) based on other data in the application if the product meets one of the following criteria: (1) The drug product: (i) Is a parenteral solution intended solely for administration by injection...; AND (ii) Contains the same active and inactive ingredient in the same concentration as a drug product that is the subject of an approved full NDA. (2)...

2. The effect of volume of injection was tested in NDA 20-246, Depo-Provera Contraceptive Injection. An enhanced rate of absorption was observed with higher injection volume (lower concentration).

3. Dr. Lisa Rarick, Division Director, DRUDP (HFD-580) indicated that the reliability of the "switchability" (2 x 75 IU/vial versus 1 x 150 IU/vial) of the 75 and 150 IU vials is of clinical significance and the recommendation for an in vivo BE study was supported by the clinical division.

In a teleconference between the Agency and Organon on March 25, 1997, it was learned that up to or vials of Follitropin can be dissolved in ml diluent. In the pivotal clinical trials submitted to NDA 20-582 on January 9, 1996 when multiple vials (75 IU/vial) of Follitropin were needed to achieve the desired dose, the following procedure was used;

Therefore, the total volume of injection was ml.

Additionally, it was learned that Follitropin will be labeled to indicate the aforementioned dissolution procedure and that up to may dissolved in ml diluent.

On January 9, 1997, Organon Inc. submitted an amendment to NDA 20-582 to address OCPB/DPE II concerns about the 150 IU vial of Follitropin. The submission contains the study report of a multiple dose, pharmacokinetic study to assess the dose proportionality of 75, 150 and 225 IU doses of Follitropin, in which each dose was reconstituted in ml of solvent and injected subcutaneously. Therefore, this report also addresses the effect of varying the concentration of injection from IU/ml.

STUDY SUMMARY

Study Number: 37624

Title: An open, group-comparative, randomized, multiple-dose study to assess the dose-proportionality of subcutaneously administered Follitropin and to compare the pharmacokinetics of Follitropin administered by subcutaneous and intramuscular routes in healthy female volunteers.

Objective: The primary objectives were to determine the pharmacokinetics and dose proportionality of Follitropin administered via the subcutaneous route in a multiple-dose regimen and to compare the pharmacokinetics of 150 IU Follitropin administered once daily via the subcutaneous and intramuscular route.

Study Design: This was a randomized, single-center, group-comparative, multiple-dose study.

Subjects: Forty-eight healthy female subjects, 18 to 39 years of age, weighing 50 to 75 kg, maintained on oral contraceptives for at least 3 months.

Formulations: The formulation used in this study is the to-be-marketed 75 IU formulation and is included in Table 1.

DEC 12 1996

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-582

Compound: Follitropin Beta (Org 32489) for Injection (75 IU/vial and 150 IU/vial)

Submission Dates: 1/10/96
6/21/96 (Amendment Serial No. BZ)

Sponsor: Organon, Inc.

Types of Submission: Original NDA and Amendment

Code: 3S

Reviewer: K. Gary Barnette, Ph.D.

I. SYNOPSIS

The submission to NDA 20-582, dated January 10, 1996 is intended to support the approval of Follitropin Beta (Org 32489) for the indication of development of multiple follicles in ovulatory patients seeking assisted reproduction and induction of ovulation and pregnancy in the anovulatory infertile patient with functional infertility

The recommended starting dose for assisted reproduction therapy is 150 to 225 IU/day for at least 4 days followed by individual dose adjustment based on ovarian response A reported maintenance dose range of 75 to 600 IU/day were studied in the well controlled clinical trials (not submitted to the Division of Pharmaceutical Evaluation II) After a "sufficient number" of follicles of "adequate size" are present, a 5000 to 10,000 IU dose of human chorionic gonadotropin (hCG) is administered, unless the ovaries are enlarged where hCG is withheld The recommended starting dose for ovulation induction in anovulatory infertile patients with functional infertility is 75 IU/day for at least 7 days If no ovarian response, the dose will be gradually increased until follicular growth and/or serum estradiol levels indicate adequate response. The recommended dosing range for this indication is 75 to 300 IU/day

This submission contains five evaluable pharmacokinetic studies, none of which were conducted in the US. The absolute bioavailability of intramuscular and subcutaneous administration of Org 32489 compared to an intravenous route of administration in normal, healthy, downregulated female volunteers was assessed in Study 37614. The comparative pharmacokinetics and pharmacodynamics of Org 32489 with currently marketed FSH formulation, Metrodin® during a single dose regimen in gonadotropin deficient males and females and a multiple dose regimen in normal, healthy downregulated female volunteers were assessed in Studies 37601 and 37607, respectively. Study RM-9211 contained two parts, a single dose pharmacokinetic study followed by a multiple dose rising pharmacokinetic and pharmacodynamic assessment in gonadotropin deficient Japanese females. An inter-study comparison was made to assess a race based difference in PK between Study RM-9211 (Japanese subjects) and Study 37601 (European subjects). The final study (Study 37602) is a pharmacokinetic and pharmacodynamic assessment Org 32489 in gonadotropin deficient males and females during a multiple rising dose regimen.

An amendment to NDA 20-582 was submitted on June 21, 1996 in response to a letter dated March 4, 1996 from the Division of Reproductive and Urologic Drug Products (HFD-580) requesting additional clinical pharmacological and biopharmaceutical information.

II. RECOMMENDATION

NDA 20-582, submitted on January 10, 1996, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). It is the opinion of OCPB/DPE II that the sponsor has provided appropriate information to satisfy the clinical pharmacology and biopharmaceutic regulations outlined in 21 CFR 320 for the **75 IU vial of Org 32489**.

Since a change in total injection volume/concentration of parenteral injections has been shown to alter bioavailability and the proposed to-be-marketed 150 IU/1 mL diluent formulation was not used in any of the clinical or pharmacokinetic trials, based on clinical pharmacology and biopharmaceutic regulations (21 CFR 320), it is the recommendation of OCPB/DPE II that approval of this formulation strength be withheld pending the conduct, submission and review of a proper *in vivo* bioequivalence study comparing the 75 IU/vial and 150 IU/vial formulation strengths. The proposed protocol for this recommended study should be submitted to the Agency for review prior to initiation.

Based on the current OCPB/DPE II format, the **Clinical Pharmacology** section of the proposed package insert appears appropriate and is accepted provided following changes are incorporated

The recommendation and comments should be communicated to the sponsor as appropriate.

K Gary Barnette, Ph.D.
Office of Clinical Pharmacology and Biopharmceutics
Division Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 12/3/96
FT signed by Angelica Dorantes, Ph.D., Team Leader 12/12/96

cc: **NDA 20-582, HFD-580 (Bennet,Pauls), HFD-870 (ML.Chen, Hunt, Dorantes, Barnette), HFD-340 (Viswanathan), Drug file, Chron file, Review (Clarence Bott, HFD-870, PKLN Rm. 12A-43).**

TABLE OF CONTENTS:

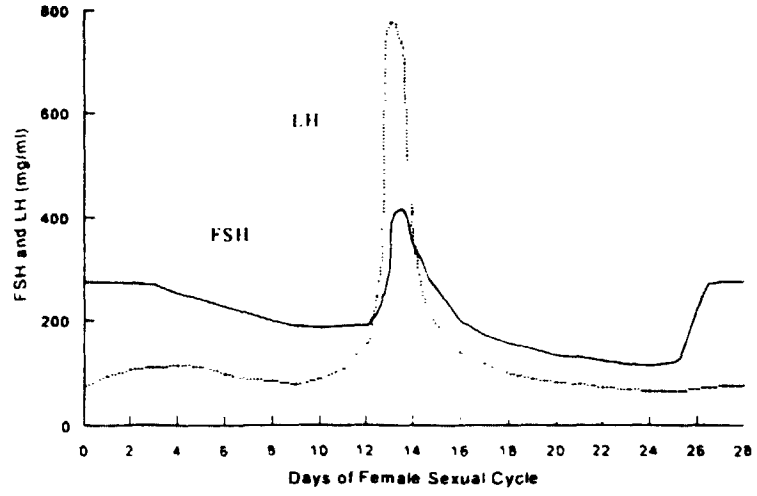
III. BACKGROUND

Human follicle stimulating hormone (hFSH) derived from the urine of postmenopausal women has been marketed for over 30 years. Metrodin® (urofollitropin for injection) is currently marketed for the indication of induction of ovulation in patients with polycystic ovarian disease who have elevated LH/FSH ratio and to stimulate the development of multiple oocytes in ovulatory patients participating in an *in vitro* fertilization program. Follitropin Beta (Org 32489) is recombinant follicle stimulating hormone (rFSH) produced by Chinese hamster ovary cells. The primary and tertiary amino acid sequence and structure of the resulting rFSH is identical to those of natural human FSH (hFSH). However, there are slight differences in the carbohydrate chain structures between rFSH and hFSH.

The scientific rationale for a recombinant formulation of FSH for these indications is that due to the nature of collection and extraction of the hFSH from urine, the availability of these preparations are limited and the biochemical purity of such preparations is questionable. Org 32489 is reportedly ≥99% pure, the availability of the product is essentially endless and biochemically almost identical to urine-extracted hFSH.

For reference, FSH and LH levels during the menstrual cycle in a normal ovulating female are included in Figure 1, below.

Figure 1. FSH and LH levels During Normal Menses



Ovulation on Day 14

VI. Analytical Methodology

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Comments:

1 The assays used appear appropriate and overall the validations presented are accepted See individual study summaries for the comments on the validation for each study

VII. Pharmacokinetic/Pharmacodynamic Studies

Pharmacokinetic Study Summary

Study #	Design	Dose	Population	Page #
37614	Randomized,open,single dose,three-way crossover, single center	300IU IV,IM and SC	19♀ pituitary suppressed	30
37601	Open,single dose, multicenter	300IU IM vs Metrodin® 300IU IM	8♀/7♂	33
RM-9211	Open,non-comparative multicenter	Part I Single Dose 300IU IM Part II Multiple Dose 75IU/day; 150IU/day, 225IU/Day, IM each dose x 7 days	Part I 5♀ Part II 4♀	36
37607	Randomized,open,group-comparative,multiple dose,single center	ORG 32489 Group 1 75 IU/day IM Group 2 150 IU/day IM Group 3 225 IU/day IM Metrodin® Group 4 150IU IM	36♀ (9/group, pituitary suppressed)	44
37602	Open,multiple rising dose multicenter	75-225IU IM daily using weekly rising doses	7♀/9♂	48

A. Pharmacokinetics

Absolute Bioavailability

Study 37614 was a single dose, randomized, three-way crossover study in pituitary suppressed (Lyndiol®) healthy females. The bioavailability of the IM and SC routes of administration compared to an IV route were assessed.

Table 3. Pharmacokinetic Parameters

Study #	Route of administration	Dose (IU)	n	AUC0-312 (IU*h/L)	Cmax (IU/L)	Tmax (h)	F (%)
37614	IV	300	13	587 8 ± 202 7	42 99 ± 3 89	----	----
	IM	300	13	445 7 ± 135 7	6 86 ± 2 90	18 15 ± 10 15	76 4
	SC	300	13	455 6 ± 141 4	5 41 ± 0 72	17 38 ± 7 68	77 8

Comments:

1 The absolute bioavailability of Org 32489 from IM and SC routes of administration are 76 4 and 77.8%, respectively

Relative Bioavailability

In Study 37614, an additional bioavailability comparison between the IM and SC was made. The pharmacokinetic parameters for this study can be seen in Table 3, above The mean FSH blood levels are depicted in Figure 2 and the statistical comparison of the IM and SC routes of administration is outlined in Table 4, below.

Figure 2.

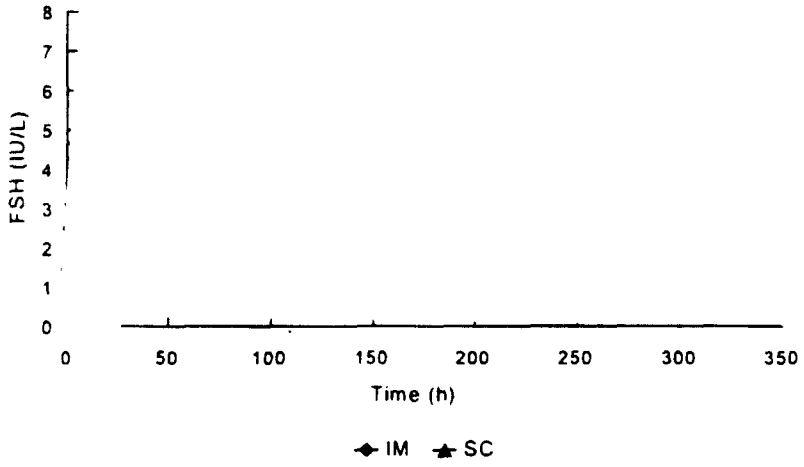

Table 4.

	90% CI (log transformed)
Cmax	71 8 - 101
AUC	94 3 - 110

Two relative bioavailability studies between Org 32489 and Metrodin® were performed (Studies 37601 and 37607). Study 37601 was a single dose PK study in gonadotropin deficient subjects. This study was NOT a crossover study and Org 32489 was given followed by Metrodin® after an 11 day washout period. Study 37607 was a multiple dose, parallel study in pituitary suppressed (Lyndiol®) healthy females. The mean FSH blood levels from Study 37607 are depicted in Figure 3 and the pharmacokinetic data summary for both studies is included in Table 5.

Figure 3

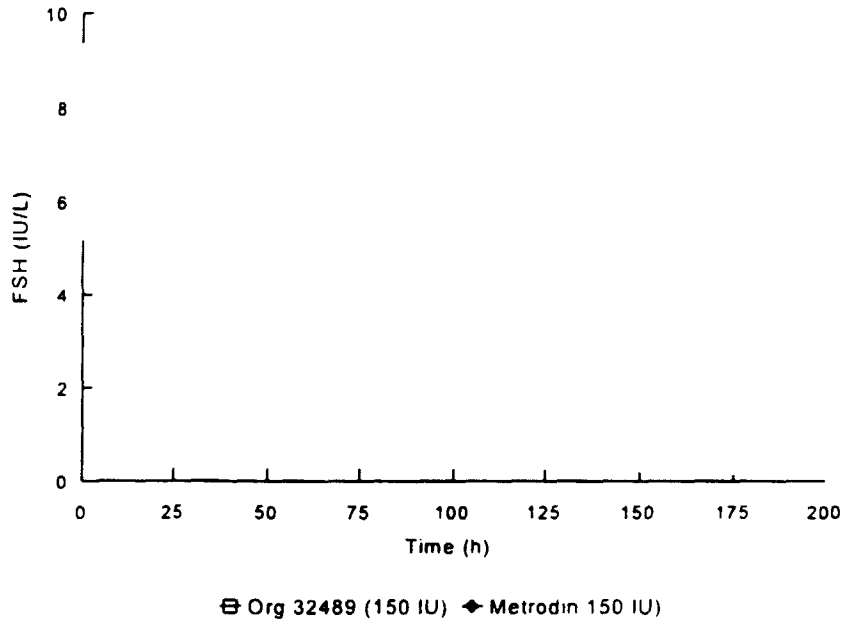

Table 5. Pharmacokinetic Parameters

Study #	Formulation	Dose	n	AUC# IU*h/L	Cmax IU/L	Tmax (h)	T½ (h)
37601 (single dose)	Org 32489	300 IU	8	339 ± 105	4 3 ± 1 7	26 9 ± 5 4	43 9 ± 14 1
	Metrodin®	300 IU	5	547 ± 127	7 2 ± 2 3	21 1 ± 10 9	37 6 ± 9 3
37607 (multiple dose)	Org 32489	150 IU/day	7	203.68 ± 49 29	9 46 ± 2 57	10 86 ± 6 31	30 1 ± 6 22
	Metrodin®	150 IU/day	8	231 14 ± 44 45	10 70 ± 2 03	4 76 ± 3 00	30 3 ± 4 1

The time intervals for the two studies are different; Study 37601 = $AUC_{0-\infty}$, Study 37607 = AUC_{0-24}

The apparent bioavailability of Org 32489 (300 IU single dose) compared to Metrodin® (300 IU single dose) is 0 66 (see Comment #1)

The statistical comparison of bioavailability from Study 37607 is outlined in Table 6

Table 6

	90% CI
AUC0-24	79-114
Cmax	79-119

Comments:

1 There is evidence from Study RM-9211 that 11 days after the last Org 32489 dose that FSH levels had NOT returned to baseline. Therefore, the data from Study 37601 may under estimate the bioavailability of 300 IU dose of Org 32489 compared to the 300 IU dose of Metrodin®.

2 The statistical comparison of AUC and Cmax from Study 37607 indicates similar bioavailabilities between Org 32489 (150 IU/day multiple dose) and Metrodin® (150 IU/day multiple dose)

3 Additionally, the comparative bioavailability of Org 32489 from IM and SC routes of administration indicates that while extent of absorption is equivalent between the IM and SC injections, rate of absorption appears statistically different (Cmax IM > Cmax SC).

Diluent Volume/FSH Concentration Effect

The volume of diluent used in Studies 37601, 37607, and RM-9211 was the to-be-marketed volume, 1 mL However, the volume used in Studies 37602 and 37614 was 0.5 mL. A between study comparison of the pharmacokinetics of the 75 IU/vial (300 IU total dose) dissolved in 1 mL delivered by IM injection (Study 37601) and the 75 IU/vial (300 IU total dose) dissolved in 0.5 mL also delivered by IM injection (Study 37614) was made by this reviewer. The results of this comparison and the deficiencies in such a comparison are outlined in Table 2 and Comment 2.

Table 2 Pharmacokinetic Comparison; Both Total Doses = 300 IU, Given by IM Injection

Study #	Diluent Volume/Vial (mL)	Subject Weight (kg)*	n	AUC (IU×h/L)#	Cmax (IU/L)	Tmax (h)
37614	0 5	64 (53-72)	13 ♀ - downregulated with Lyndiol®	445 7 ± 135 7	6 86 ± 2 90	18 15 ± 10 15
37601	1 0	67 (43-85)	8 ♀ - gonadotropin deficient	339 ± 105	4 3 ± 1 7	26 9 ± 5 4

- AUC from Study 37614 = $AUC_{0\text{-}312}$, Study 37601 = $AUC_{0\text{-}\infty}$

* - Subject weight is reported as mean (range)

Comments:

1 It is acknowledged that the study populations from Studies 37614 and 37601 are different, normal healthy volunteers, downregulated with Lyndiol® and gonadotropin deficient subjects, respectively However, the observed differences in AUC, Cmax and Tmax between the two studies could be due to the different diluent volume used and/or the different concentrations of FSH used in each of the studies. It should be noted that the proposed to-be-marketed 150 IU formulation injection will necessitate a different total injection volume and FSH concentration than the clinically tested 75 IU formulation, i e. if the desired dose is 300 IU, the total injection volume using the 75 IU formulation will be 4 mL and only 2 mL using the 150 IU formulation. Therefore, the data presented in Table 2, above, further indicate the importance of the biopharmaceutical information to support the approval of the 150 IU vial that is not presented in this submission

Dose Proportionality

The pharmacokinetic dose proportionality of Org 32489 was assessed in a multiple rising dose study (Study 37607) over a dosing range of 75 to 225 IU/day This study was conducted in pituitary suppressed (Lyndiol®) healthy females. The mean FSH blood levels from the three doses are depicted in Figure 4 and the pharmacokinetic parameters in Table 7.

Figure 4

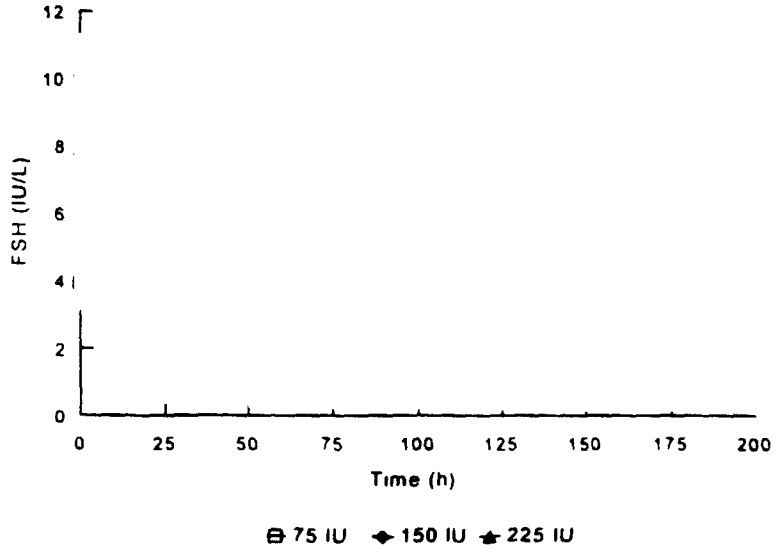

Table 7 Pharmacokinetic Parameters

Study #	Dose	n	AUC0-24 (IU*h/mL)	Cmax (IU/mL)	Tmax (h)	T½ (h)
37607	75 IU	9	96 70 ± 22.28	4 65 ± 1 49	8 21 ± 4 29	26 8 ± 7 8
	150 IU	7	203 68 ± 49.29	9 46 ± 2.57	10 86 ± 6 31	30 1 ± 6 22
	225 IU	8	242 37 ± 44 12	11.30 ± 1 77	11.25 ± 8 04	28 9 ± 6 5

Table 8 Dose Proportionality Comparative Analysis

	Dose adjusted Values		
	75 IU	150 IU	225 IU
AUC (IU hr/L)	1 50 ± 0 35	1 58 ± 0 38	1 25 ± 0.23
Cmax (IU/L)	0 072 ± 0.23	0 073 ± 0.020	0 059 ± 0 009

Comments:

1 Dose proportionality was observed between the 75 IU/day and 150 IU/day doses However, the 225 IU/day dose is not dose proportional with the other two doses A plausible reason for the lack of dose proportionality between these doses of Org 32489 is saturable binding phenomenon that the 225 IU/day dose exceeds.

2 The proposed dosing range in the proposed labeling is 75 to 600 IU/day The above dose proportionality study is only from 75 to 225 IU/day and single dose PK of 300 IU has been submitted It was requested in the letter from HFD-580, dated March 4, 1996 that dose proportionality over the entire proposed dosing range should be submitted. In the response from the sponsor, submitted June 21, 1996 it was stated that only 10% of the subjects in the clinical studies needed doses above 300 IU/day to achieve the desired pharmacodynamic effects (follicle maturation) It was also stated that doses from 75 to 600 IU/day were used safely and effectively in the clinical trials and that "overdosing" subjects with FSH for the sake of a pharmacokinetic dose proportionality data is unethical I concur with the sponsor's response and believe that the dose proportionality of FSH from 75 to 600 IU is not clinically relevant, since dose escalation with patient monitoring is indicated clinically

B. Pharmacodynamics

Summary data for the development of mature follicles (≥15 mm in diameter) after administration of Org 32489 and Metrodin®/Humegon™ from the clinical trials were submitted in Section 6 (complete data were not submitted to OCPB/DPE II) and is presented in Table 9. The dosing range used to achieve these results was between 75 and 600 IU/day, but the individual doses were not submitted to OCPB/DPE II

Table 9. Mean Number (n) of Mature Follicles per Subject at the Completion of FSH Treatment

Study number		Org 32489	Metrodin®/Humegon™
Indication Controlled Ovarian Hyperstimulation for Assisted Reproductive Technology			
37608	Cycle 1	8.0 (545)	7 3 (361)
	Cycle 2	7 4 (196)	7 2 (149)
	Cycle 3	7.2 (53)	7.1 (53)
37604		5.5 (48)	5 4 (32)
37611		7 7 (53)	7 0 (31)
37613	IM	8 1 (73)	na
	SC	8 8 (112)	na
37617	IM	12.7 (6)	9.7 (7)
	SC	11.0 (7)	na
37603	Group I	4.2 (9)	na
	Group II	5 3 (9)	na
	Group III	5.3 (11)	na
	Group IV	5.1 (11)	na
	Group V	7 0 (10)	na
Indication Classical Ovulation Induction (objective was to achieve monofollicular growth)			
37609	Cycle 1	2.0 (105)	1 7 (66)
	Cycle 2	2.0 (69)	1.6 (42)
	Cycle 3	2.6 (49)	1 4 (29)

na = not applicable

Study 37602 was a multiple rising dose pharmacokinetic/pharmacokinetic study in gonadotropin deficient females The PK/PD data from this study are included in Table 10.

Table 10.

Sub #	Diagnosis	Doses Received (IU/day)	Estradiol (pmol/mL)		FSH (IU/L)		Follicles	
			Pre-level	Maximum level	Pre-level	Maximum level	Maximal Size (mm)	n
	hypophysectomy	7 x 75 7 x 150 7 x 225	7 6	112 1	0 07	8.32	11 - 13	1
	hypophysectomy	7 x 75 7 x 150 7 x 225	NA	18.0	0.10	8 79	<8	2
	hypophysectomy	7 x 75 7 x 150 7 x 225	NA	48 5	<0 05	9 94	None	0
	idiopathic	7 x 75 5 x 150	32 3	210 0	1 15	8 46	>17	3
	idiopathic	7 x 75 7 x 150 7 x 225	<5 1	76 7	0 56	11 8	>17	1
	idiopathic	7 x 75 7 x 150 3 x 225	37 7	139 5	1 07	10 1	>17	1
	idiopathic	7 x 75 7 x 150 2 x 225	11 1	42 6	0 25	7 13	14 - 16	1
Normal Range (follicular phase)			147 - 1470		2 4 - 9 3			

Comments:

1 The clinical dose titration will be justified by the measurement of maturing follicles and serum estradiol levels

2 It is apparent from the data presented (titrated dose required, # and diameter of maturing follicles) that the interindividual variability of response (development of mature follicles) is great

3 From the summary of the follicle maturation from the clinical trials (Table 9), Org 32489 appears to be as efficacious as currently marketed urofollitropins

C. Metabolism

Org 32489 (recombinant FSH) is very similar to human/endogenous FSH and should be metabolized in a similar manner.

D. Special Populations

Body Weight/Race.

The effect of body weight and race on the pharmacokinetics of Org 32489 was evaluated in a group of European (Study 37601) and Japanese women (Study RM-9211) who were significantly different in terms of body weight The pharmacokinetic parameters and statistical p-value from single, IM doses of 300 IU Org 32489 from these two studies is outlined in Table 11

Table 11

	Japanese (n=5)	European (n=8)	p-value
Weight (kg)	46 8 ± 11 6	67 4 ± 13.5	**0.0172**
Cmax (IU/L)	6 82 ± 3 3	4 30 ± 1.7	0 0880
Tmax (h)	23.2 ± 16 0	26.9 ± 5.4	0 2275
t½ (h)	38 4 ± 18 3	43 9 ± 14.3	0.4100
AUC0-∞ (IU×h/L)	544 ± 201	339 ± 105	**0.0303**

The possible effect of race resulting in the differences in AUC0-∞ were ruled out with a weight normalized estimate of clearance, Table 12

Table 12

	Japanese (n=5)	European (n=8)	p-value
Cl/kg (L/h/kg)	0.013 ± 0 0018	0 014 ± 0 0021	0 3365

Comments:

1 This analysis indicates that body weight is most likely the major effector of the differences in AUC0-∞ seen in this inter-study comparison and race, at most plays a limited role.

2 It should be noted that the pharmacokinetics of Org 32489 in African/African American compared to the European and Japanese population has not been made.

3 The data presented in "**D. Special Population**, *Body Weight/Race*" section above, are included in the proposed labeling for Org 32489 The clinical significance of these data, however, is limited since individual dose adjustment, based on pharmacodynamics (development of mature follicles and serum estradiol levels) will be used

VIII. Labeling

The proposed labeling is included in Attachment 1

14 Pages (15-28)
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Appendix 1

Individual Study Summary

Study Number: 37614

Study Title: An Open Three-Way Crossover, Comparative Pharmacokinetic Study in Healthy Female Pituitary-Suppressed Volunteers to Assess the Absolute Bioavailability of a Single Dose of 300 IU ORG 32489 After Intramuscular and Subcutaneous Injection

Investigator:

Objectives: To assess the bioavailability of Org 32489 after intramuscular (IM) and subcutaneous (SC) injection in comparison to intravenous (IV) administration in female volunteers of reproductive age.

Study Design: This was an open, single dose, single-center, randomized, three-way cross-over study in pituitary-suppressed women.

Subjects: The study population consisted of 15 normal female volunteers with the following demographic characteristics.

Table 1 Patient Demographics

	Age (years)	Weight (kg)	Height (cm)	Menstrual Cycle Length (days)
Mean (range)	30	64	168	28

Formulation: The formulation used in this study was the to-be-marketed IU formulation. However, the volume of diluent used in this study mL) is NOT the to-be-marketed volume mL). The composition of the formulation is included in Table 2

Table 2 To-be-marketed 75 IU Formulation composition

Ingredient (units)	75 IU vial
r-hFSH (IU/vial)	75
Sucrose (mg/vial)	25
Polysorbate 20 (mg/vial)	0 1
Sodium Citrate (mg/vial)	6 45
Diluent 0 45% NaCl (ml)	0 5
HCL and or NaOH	Adjust pH to
Water for Injection	Trace

Dosage and Administration: This study is an absolute bioavailability study comparing the pharmacokinetics of subcutaneous (right or left lower quadrant of the abdominal wall), intramuscular (upper right lateral quadrant of the buttock) and intravenous (into a forearm vein) routes of administration The subjects were randomized to the sequence in which the received each route. However, each dose, regardless of the route of administration was 300 IU (4 × 75 IU vial injections).

It should be noted the Lyndiol® was administered to downregulate/suppress endogenous FSH release and levels The following dosing regimen was followed:

Table 3 Dosing Schedule

Study Day(s)	Lyndiol® Dose (mg/day)	Org 32489 Dose (IU)
1-56	2.5 lynestrenol 0.05 ethinyl estradiol	
15		300 (route 1)
29		300 (route 2)
43		300 (route 3)

Blood Sampling: Blood samples were obtained at the following times corresponding to the route of administration. *Intravenous*: -24 hours, and -15 minutes pre-dose, and 5, 10, 15, 20, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96, 120, and 144 hours post-dose. *Subcutaneous/Intramuscular*: -24 hours, and -15 minutes pre-dose, and 0.5, 1, 1 5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, 48, 72, 96, 120, 168, 216, 264, and 312 hours post-dose.

Analytical Methodology and Validation:

Table 4 Quality Control FSH

	QC-low (4 59 IU/L)	QC-medium (9 92 IU/L)	QC-high (30 0 IU/L)
Mean	4 59	9.54	29 3
Intra-assay Precision	%	%	%
Inter-assay Precision	%	%	%
Accuracy	%	%	%

Table 5 Quality Control LH

	QC-low (3 19 IU/L)	QC-medium (16 8 IU/L)	QC-high (51 1 IU/L)
Mean	3 35	16 5	50 2
Intra-assay Precision	%	%	%
Inter-assay Precision	%	%	%
Accuracy	%	%	%

Results:

The pharmacokinetics of single doses of 300 IU Org 32489 by IV, IM and SC routes of administration are included in Table 6 The statistical comparison of the IM and SC routes of administration is outlined in Table 7

Table 6

	Route of Administration		
	IV	IM	SC
f (%)		76 4	77 8
Cmax (IU/L)	43.0 ± 3 9	6.9 ± 2.9	5 4 ± 0.7
Tmax (h)	NA	18.2 ± 10 2	17 4 ± 7 7
AUC 0-312 (IU×h/L)	588 ± 203	446 ± 138	456 ± 141

Table 7 SC vs. IM Statistical Comparison

	SC	IM	90% CI (log transformed)
Cmax	5 41 ± 0 72	6.86 ± 2.90	71 8-101
AUC	456 ± 141	446 ± 138	94 3-110

Sponsor's Conclusions:

1 Org 32489 is safe and well tolerated following a single dose of 300 IU by SC, IM and IV routes, in female volunteers, using the oral contraceptive, Lyndiol®.

2 The SC and IM administration were bioequivalent with respect to the extent (AUC0-312) of absorption. However, probably due to large intra-subject variability, bioequivalence could not be proven statistically with respect to the rate of absorption.

Reviewer Comments:

1 The possibility of interaction between Org 32489 and Lyndiol® was not addressed in this study

2 The SC and IM routes of administration are not bioequivalent, due to differences in the rate of absorption

3 It should be noted that AUC0-∞ was not calculated and AUC0-312 was used in these calculations The mean ± SD FSH (IU/L) levels at 312 hours post-dose are 0.58 ± 0.82 and 0.40 ± 0.66 for SC and IM, respectively. It is unclear why the sponsor did not attempt to assess AUC0-∞ from these data Consequently, the relative bioavailability of Org 32489 after SC and IM administrations compared to IV may be under reported at 77.8% and 76 4%, respectively.

4 It should also be noted that Study 37614 was conducted in Sweden. Therefore, the study population used in herein was of Swedish descent.

Study Number: 37601

Study Title: An Open Phase I Study in Gonadotropin Deficient, but Otherwise Healthy, Subjects to Assess the Tolerance and Safety of a Single Intramuscular Dose of ORG 32489 and to Compare its Pharmacokinetic and Pharmacodynamic Properties with Metrodin®

Investigators:

Objectives:

- To establish the safety and tolerance of a single, 300 IU, intramuscular dose of Org 32489.
- To establish the PK and PD properties of Org 32489 compared to Metrodin®
- To compare the PK properties of Org 32489 in gonadotropin deficient men and women

Study Design: This was a multi-center, open, single dose study A total of 10 subjects (4 males and 6 females) received Org 32489 then after an 11 day (minimum) washout period received a 300 IU dose of Metrodin® (75 IU hFSH/ml)

Subjects: The study population consisted of 7 male and 8 female gonadotropin deficient subjects in good general health with the following demographic characteristics

Table 8 Patient Demographic. Mean (range)

Gender	Age (years)	Weight (kg)	Height (cm)
Female	35 6 (33-42)	67.3 (43-85 8)	161 5 (138-180)
Male	30 7 (19-41)	62 0 (42 3-76 5)	171 1 (145-188)

Formulation: The formulation of Org 32489 used in this study was the to-be-marketed 75 IU formulation

Dosage and Administration: This study was a comparative bioavailability study comparing the pharmacokinetics of Org 32489 with the currently marketed Metrodin® both given by IM injection to the upper lateral quadrant of the buttock A 300 IU FSH dose was delivered regardless of the product However, it is stated that a total solvent volume of 2 ml was used for Org 32489 and either 2 or 4 ml was used with Metrodin®. The reason for the two different volumes for Metrodin® is unknown

Blood Sampling: Blood samples were obtained at 0 (prior to dose) and 0.5, 1, 1.5, 2. 3. 4. 6. 7. 8. 9, 10, 12, 16, 24, 36, 48, 72, 96. 120. 168, 216 and 264 hours post-dose

Analytical Methodology and Validation:

Table 10 Quality Control FSH

N	Each sample was run in triplicate
Intra-assay CV	%
Inter-assay CV	%
Sensitivity (mean ± SEM of 5 experiments)	3 7 ± 1 1 IU/L

Results:

Table 11.

	Male		Female		Statistics (ANOVA, p-values)	
	Org 32489	Metrodin®	Org 32489	Metrodin®	Male vs Female	Org vs Metrodin®
Cmax (IU/L)#	7 4 ± 2 8	11 6 ± 1 7	4 3 ± 1 7	7 2 ± 2 3	**0.0072**	**0.0002**
Tmax (h)	14 3 ± 7 5	9 2 ± 2 1	26.9 ± 5.4	21 1 ± 10.9	**0.0004**	0 3778
T½ (h)#	32 1 ± 11 6	43 3 ± 9 9	43.9 ± 14 1	37 6 ± 9 3	0 2685	0 2785
AUC0-∞ (IU×h/L)#	452 ± 183	764 ± 190	339 ± 105	547 ± 127	0 0582	**0.0001**
n	6	4	8	5		

- baseline ADJUSTED values

Sponsor's Conclusions:

1 The rate of absorption differs between males and females (Cmax 69% higher, Tmax 50% lower in males).

2 FSH from Metrodin® appears to be more bioavailable than Org 32489 (AUC 66% and Cmax 64% higher)

Reviewer Comments:

1 This study was NOT a crossover design since Metrodin® was consistently given after Org 32489 Therefore, the effect of sequence of administration can not be assessed

2 The single dose pharmacokinetics assessed in study RM-9211 suggest that FSH levels do NOT return to baseline by 11 days post-dose. Therefore, this bioavailability comparison between Org 32489 and Metrodin® is not valid. The estimate of ≈66% bioavailability of FSH from Org 32489 compared to Metrodin® is most likely an under estimate of the true comparative bioavailability

Study Number: RM-9211

Study Title:
PART 1: An open phase I study in gonadotropin deficient but otherwise healthy female Japanese subjects to assess the pharmacokinetics of a single intramuscular dose of 300 IU Org 32489 and to compare its pharmacokinetics with those assessed in European women
PART 2. A multiple rising dose study with Org 32489 in gonadotropin-deficient Japanese women

Investigators:

Objective: To assess the pharmacokinetics of a single dose of Org 32489 in Japanese women and to compare the pharmacokinetics with those in European women and to assess the pharmacokinetics (including dose proportionality) and pharmacodynamics of multiple rising dose of Org 32489 in gonadotropin deficient Japanese females.

Study Design:
PART 1 This was an multi-center, open, single dose study
PART 2 This was a multi-center, open, multiple rising study.

Subjects: A total of 5 gonadotropin deficient (FSH and LH $\leq$2 IU/L) Japanese females were studied for single dose pharmacokinetics. These subjects were between the ages of 20 and 50 with a body weight between 80 and 130% of the standard. Four subjects (Subject [redacted] with anorexia nervosa, Subject [redacted] had a pituitectomy. Subject [redacted] with gonadotropin deficiency and Subject [redacted] with anorexia nervosa) were included in a multiple rising dose study to assess the multiple-dose rising pharmacokinetic and pharmacodynamics of Org 32489. It should be noted that 3 subjects participated in both parts (single dose and multiple rising dose) of study RM-9211

Formulation: The formulation of Org 32489 used in this study was the to-be-marketed 75 IU formulation

Dosage and Administration: In the single dose study (PART 1) 300 IU of FSH (4 vials containing 75 IU/vial) was injected be a deep intramuscular injection in the upper lateral quadrant of the buttock. During the multiple rising dose study (PART 2), a 75 IU daily dose was delivered for 7 consecutive days (Days 1-7), then escalated to a 150 IU/day dose was delivered from days 8-14, followed by 225 IU/day from days 15-21. All doses were given by deep intramuscular injection in upper lateral quadrant of the buttock

Blood Sampling: Blood samples were drawn at 0 (prior to injection) and 1, 4, 8, 12, 20, 24, 28, 32, 36, 48, 72, 96, 120, 168, 216, and 264 hours post-dose.

Analytical Methodology and Validation: No assay description or validation was submitted for this study.

Results:

Pharmacokinetics/Pharmacodynamics

Figure 1 FSH Levels Following a Single 300 IU, IM Dose of Org 32489

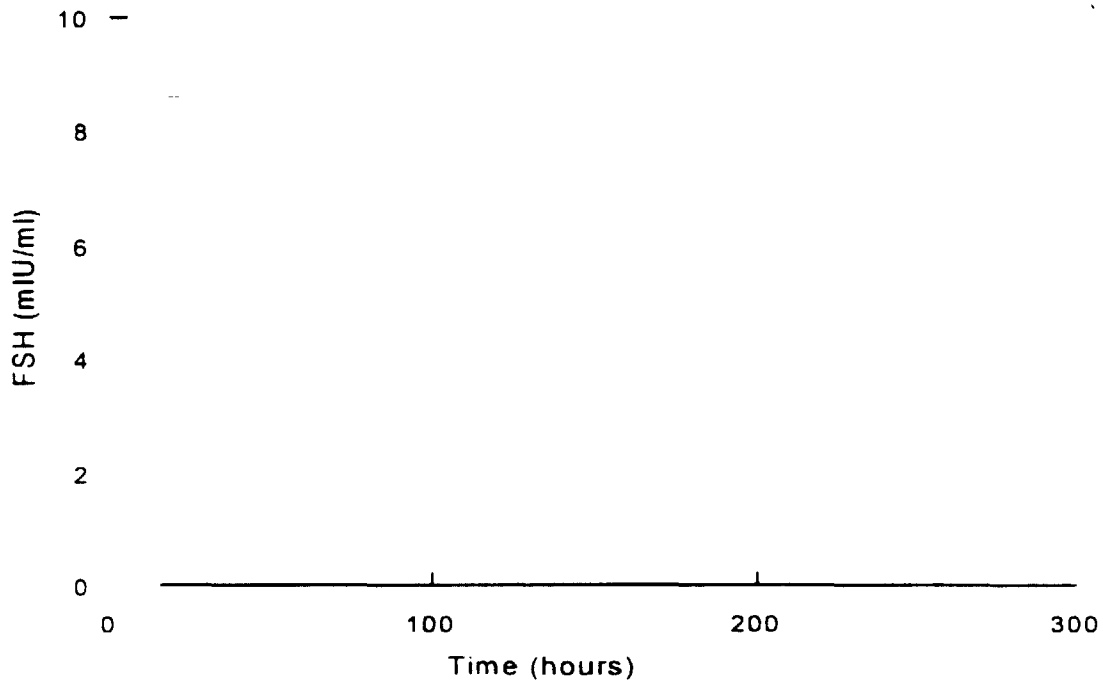

Table 13 Pharmacokinetic Parameters from Single 300 IU, IM dose of Org 32489 in Japanese Subjects (Study RM-9211) and European Subjects (Study 37601)

	Japanese (n=5)	European (n=8)	p-value
Cmax (IU/L)	6 82 ± 3 3	4 30 ± 1 7	0 0880
Tmax (h)	23 2 ± 16 0	26 9 ± 5 4	0 2275
t½ (h)	38 4 ± 18 3	43 9 ± 14 3	0 4100
Cl/kg (L/h/kg)	0 013 ± 0 0018	0.014 ± 0 0021	0 3365
AUC0-∞ (IU×h/L)	**544 ± 201**	**339 ± 105**	**0.0303**
Weight (kg)	**46 8 ± 11 6**	**67 4 ± 13 5**	**0.0172**

Table 14 Cmin Data from Multiple Rising Dose Study

	Dose	Cmin (mIU/ml)	Cmin/Dose Ratio (%)	T½ (β) (h)
Subject [redacted]				
Subject [redacted]				
Subject [redacted]				
Subject [redacted]				
Mean ± SD	75 IU	5.82 ± 1.33	7.76 ± 1.77%	51.58 ± 22.45
	150 IU	12.77 ± 5.12	8.52 ± 3.41%	
	225 IU	19.91 ± 7.12	8.85 ± 3.16%	

The individual blood profiles of FSH and estradiol are presented for each patient from the multiple rising dose in the following figures (Figures 2, 3, 4 and 5). Additionally, follicle stimulation and growth were measured by ultrasound. The results of these tests are recorded in Tables 15, 16, 17 and 18.

Subject [redacted]
Diagnosis: anorexia nervosa

Figure 2. Subject [redacted]

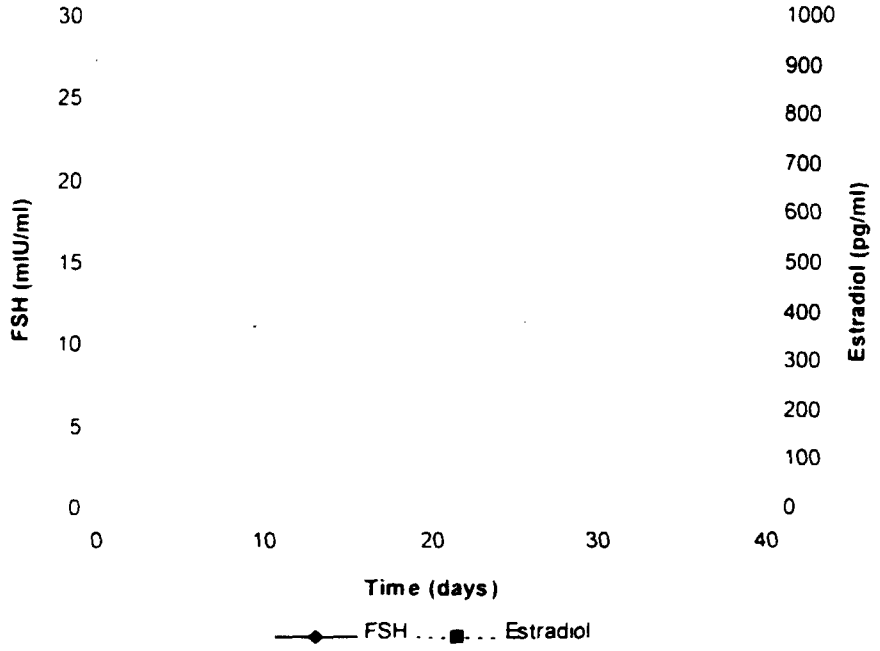

Table 15

	Day 1	Day 6	Day 8	Day 13	Day 15	Day 19	Day 22 (+1)
Dose	Prior to Dosing	75 IU	75 IU	150 IU	150 IU	225 IU	225 IU
Follicle Size (mm)	UD	UD	UD	8	10	13	22

UD = undetected

Subject [redacted]
Diagnosis pituitectomy

Figure 3

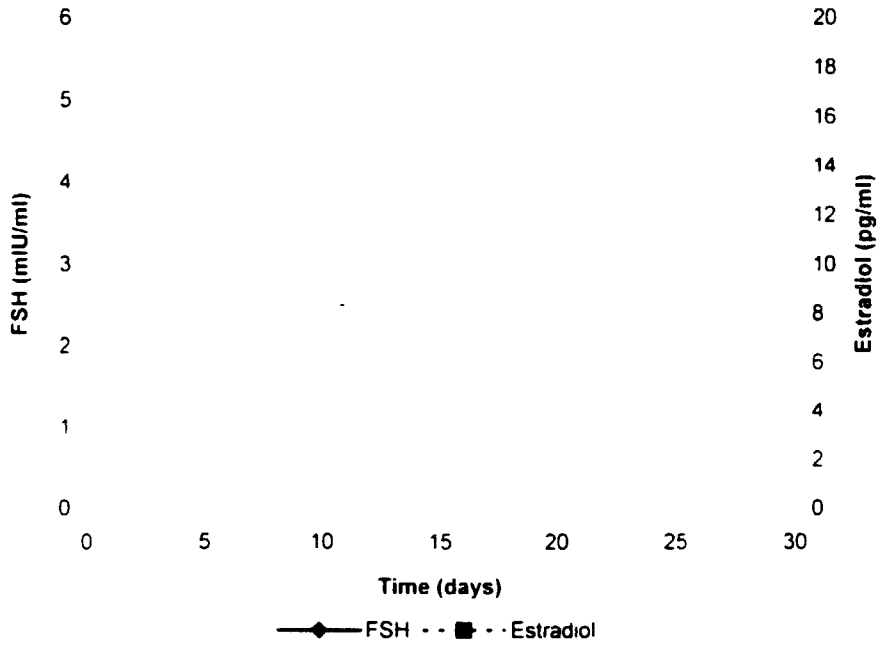

Table 16

	Day 1	Day 6	Day 8
Dose	Prior to Dosing	75 IU	75 IU
Follicle Size (mm)	UD	4 6	17.6

UD = undetected

Subject #[redacted]
Diagnosis gonadotropin deficiency

Figure 4

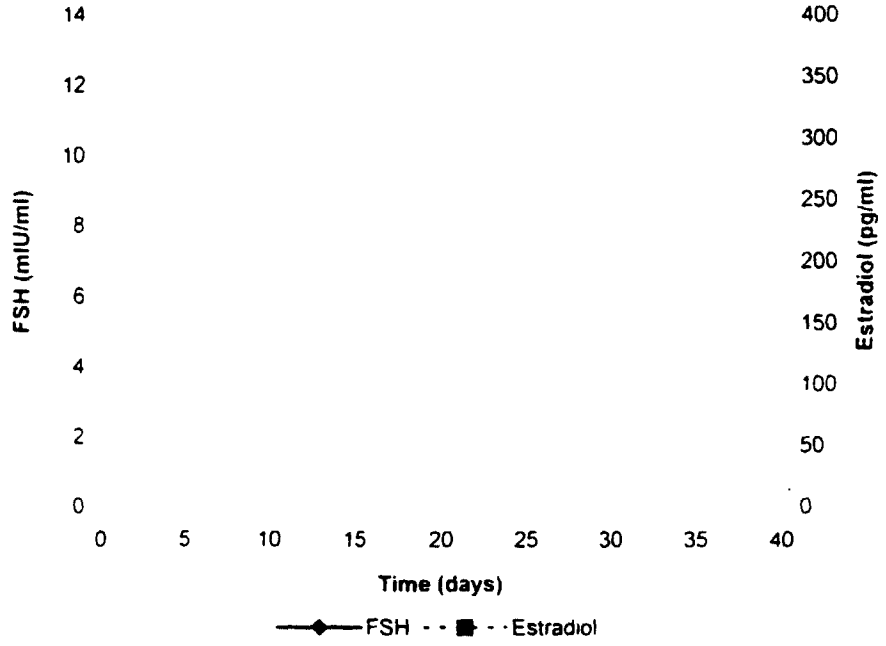

Table 17

	Day 1	Day 6	Day 8	Day 13	Day 15	Day 19
Dose	Prior to Dosing	75 IU	75 IU	150 IU	150 IU	225 IU
Follicle Size (mm)	UD	UD	UD	UD	12	20

UD = undetected

Subject [redacted]
Diagnosis anorexia nervosa

Figure 5

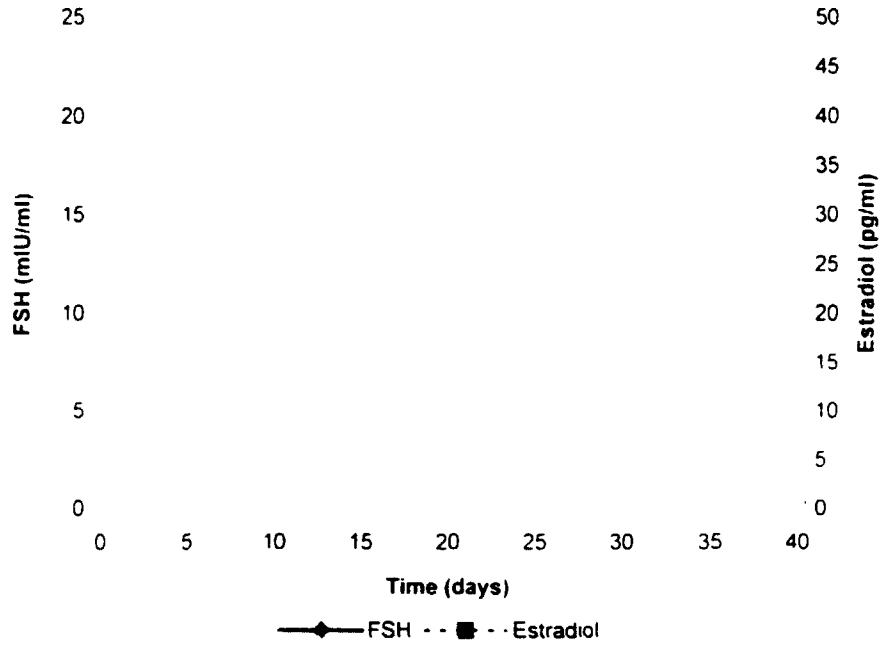

Table 18

	Day 1	Day 6	Day 8	Day 13	Day 15	Day 19	Day 22 (+1)
Dose	Prior to Dosing	75 IU	75 IU	150 IU	150 IU	225 IU	225 IU
Follicle Size (mm)	UD	UD	UD	UD	UD	UD	18

UD = undetected

Sponsor's Conclusions:

1 The differences in AUC0-∞ between the Japanese and European subjects are due to the differences in the body weight of the volunteers.

2 Org 32489 is clinically efficacious in the development of follicles and elevation of serum estradiol levels since with multiple rising doses of FSH, 4 volunteers developed follicles and elevation of estradiol was observed in 2 subjects.

3 Over a dosing range of 75-225 IU Org 32489 shows log-transformed, dose normalized Cmin dose proportionality.

Reviewer Comments:

1 No assay validation was provided. Therefore, the confidence one can have in the data presented herein is in question

2 It is apparent that 264 hours (11 days) post-dose that FSH levels did not return to the "baseline levels" measured at Time = 0

3 Since so few subjects are included in these studies (RM-9211 and 37601), the statistical power of these analyses is questionable

4 Since the weight normalized estimated clearance of FSH in Japanese and European subjects appears statistically equivalent. I concur with the assessment that the inter-study differences in apparent bioavailability is likely substantially due to differences in body weight However, the number of subjects included in this study precludes a valid statistical comparison

5 Org 32489 appears efficacious in causing serum estradiol levels to increase and facilitating follicle maturation

Study Number: 37607

Study Title: An open single-center, group-comparative, randomized, multiple-dose study in healthy female volunteers using Lyndiol® contraceptive pills to assess the pharmacokinetics of intramuscular Org 32489 compared to Metrodin®

Investigator:

Objectives: To determine the pharmacokinetics and pharmacodynamics , including dose proportionality of Org 32489 in a multiple-dose regimen and compare with Metrodin®

Study Design: This was a single-center, group-comparative, randomized, multiple-dose study in pituitary suppressed healthy female volunteers.

Subjects: The study population consisted of 36 healthy females with normal ovulatory function (4 groups of 9 subjects) ages 21 to 39 years. The body weight range was 50 to 75 kg and 130% of ideal body weight.

Formulation: The formulation of Org 32489 used in this study was the to-be-marketed 75 IU formulation

Dosage and Administration: Intramuscular FSH doses of 75, 150 or 225 IU were delivered for 7 days. The duration of treatment and design is outlined in Table 20.

Table 20

	Treatment	Study Days
Pre-Treatment	Pill free period	1 - 7
	Lyndiol®	8 - 28
Treatment	Org 32489 or Metrodin® + Lyndiol®	29 - 35
Post-Treatment	Lyndiol®	36 - 42
	No Medication	43 - 49

Blood Sampling: Single blood samples were obtained on Days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22 28, 29, 30, 31, 32, 33, and 34. On Day 35 blood sampling was formed at 0 (prior to dose), 1, 2, 4, 6, 8 10, 12, 16, 24 (Day 36), 30, 36 and 48 (Day 37) hours after dosing. Single blood sampling was resumed on Days 38, 39, 40, 41, 42, 45 and 49.

Analytical Methodology and Validation:

Table 21. Quality Control FSH

	QC-low	QC-medium	QC-high
Mean Concentration (IU/ml)	4 82	10 0	30 7
Intra-assay precision	%	%	%
Inter-assay precision	%	%	%
Accuracy	%	%	%

Table 22. Quality Control LH

	QC-low	QC-medium	QC-high
Mean Concentration (IU/ml)	3.24	16.5	50 0
Intra-assay precision	%	%	%
Inter-assay precision	%	%	%
Accuracy	%	%	%

Results:

The serum levels of FSH from the three doses (75, 150 and 225 IU/day) of Org 32489 are included in Figure 6 The levels comparing 150 IU doses of Org 32489 and Metrodin® are depicted in Figure 7. The data and statistical analysis from this study are outlined in Tables 23 and 24

Figure 6 Org 32489 Dose Proportionality

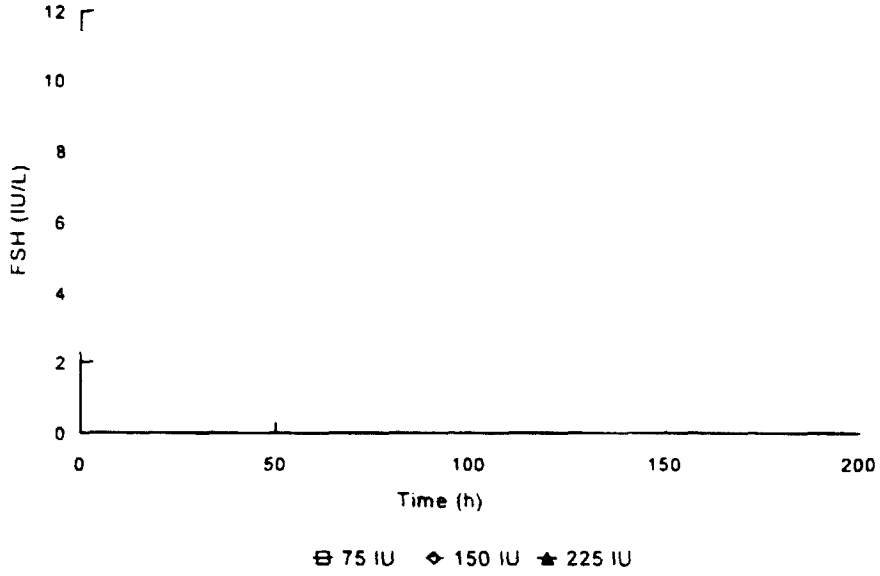

Figure 7 Comparative Blood Profiles of 150 IU Org 32489 and 150 IU Metrodin

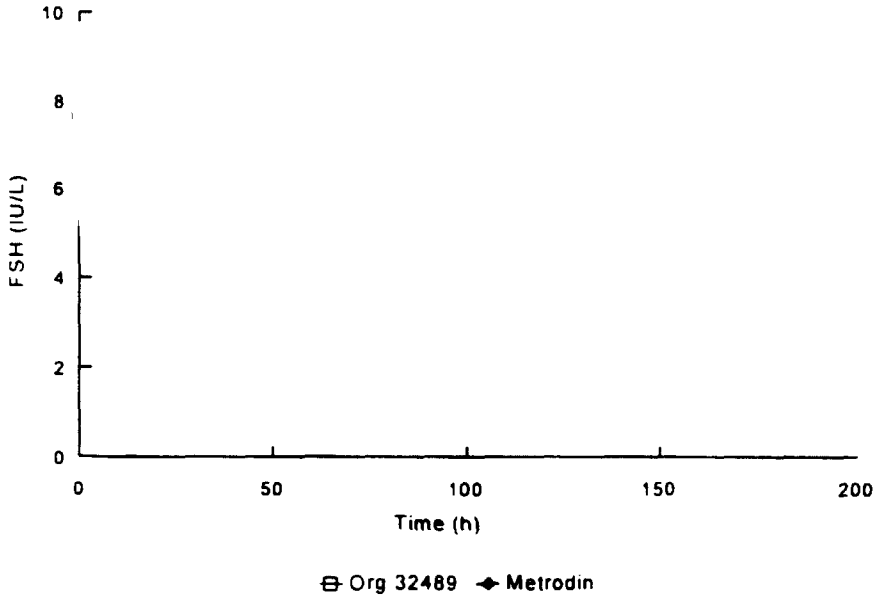

Table 23

	Org 32489			Metrodin®
	75 IU	150 IU	225 IU	150 IU
t½ (h)	26 8 ± 7.8	30 1 ± 6.22	28 9 ± 6.5	30 3 ± 4 1
Cl/kg (L/h/kg)	0 011 ± 0.002	0.010 ± 0.002	0.013 ± 0.002	0.010 ± 0 001
Cmax (IU/L)#	0 072 ± 0.023	0 073 ± 0.020	0.059 ± 0 009	0 069 ± 0 013
Baseline Adjusted Cmax (IU/L)#	0 018 ± 0 013	0.018 ± 0 012	0.008 ± 0.004	0.013 ± 0 003
AUC0-∞ (IU×h/L)#	1 50 ± 0.35	1 58 ± 0.38	1 25 ± 0.23	1 49 ± 0 29

- normalized for dose administered

Table 24 Bioequivalence statistics Org 32489 (150 IU) vs. Metrodin® (150 IU)

Parameter	90% Confidence Interval
CL/kg	91-120
AUC	79-114
Cmax	79-119

Sponsor's Conclusions:

1 Org 32489 is safe and well tolerated in females using the oral contraceptive Lyndiol®

2 Dose proportionality was not observed over the 75 to 225 IU/day dosing range. However the dose normalized pharmacokinetic parameters between the 75 and 150 IU/day doses were found proportional.

3 Borderline bioequivalence was observed between 150 IU doses of Metrodin® and Org 32489.

Reviewer Comments:

1 The lack of pharmacokinetic interaction between the formulations of FSH used in this study (Metrodin® and Org 32489) and Lyndiol® has not been proven

2 A plausible reason for the lack of dose proportionality over the 75 to 225 IU dosing range (225 IU not proportional) is the saturation of binding. However, since Org 32489 is to be titrated to an individual effective dose as determined by maturation of follicles (PD), the lack of dose proportionality is of no clinical significance.

Study Number: 37602

Study Title: An open Phase I multiple rising dose study with Org 32489 in gonadotropin deficient, but otherwise healthy, volunteers to assess its tolerance, safety, pharmacokinetic and pharmacodynamic properties

Investigators:

Objectives: To establish the pharmacokinetic and pharmacodynamic properties of Org 32489 when administered daily for 21 days using weekly rising IM doses of 75, 150 and 225 IU/day.

Study Design: This was a multi-center, multiple-dose study.

Subjects: The study population consisted of 16 gonadotropin deficient (7 females and 9 males). The patient demographics are included in Table 25.

Table 25. Mean ± SD Demographic Data (range)

	Age (yr)	Height (cm)	Weight (kg)
Females (n=7)	38 ± 7 (24-45)	159 ± 10 (142-170)	60 ± 11 (48-76)
Males (n=9)	37 ± 6 (29-50)	168 ± 13 (148-185)	65 ± 15 (42-92)

Formulation: The formulation of Org 32489 used in this study was the to-be-marketed 75 IU formulation

Dosage and Administration: Intramuscular FSH doses of 75, 150 or 225 IU were delivered to the upper lateral quadrant of the buttock for 7 days. It should be noted that the daily dose to women was suspended if the serum estradiol concentration was >200 pg/ml and a follicle of ≥14 mm was observed. Additionally, when serum estradiol levels increased above 300 pg/ml or at least one follicle ≥14 mm was observed, Org 32489 was ended

Blood Sampling: Single pre-dose blood samples were obtained on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19. Additional blood samples were drawn (after the last Org 32489 treatment) on Days 22, 24, 26, 29, 31, 33, 36 and 40

Analytical Methodology and Validation:

Table 27

	Exp I	Exp II/ 1	Exp. II/2
n	6	6	6
Repeatability (%CV)	9 6	----	4 3
Reproducibility (%CV)	10 0	5 0	4 4

Results:

Pharmacokinetics
The mean (± SD) serum levels of FSH in males and females are compared in Figure 8

Figure 8

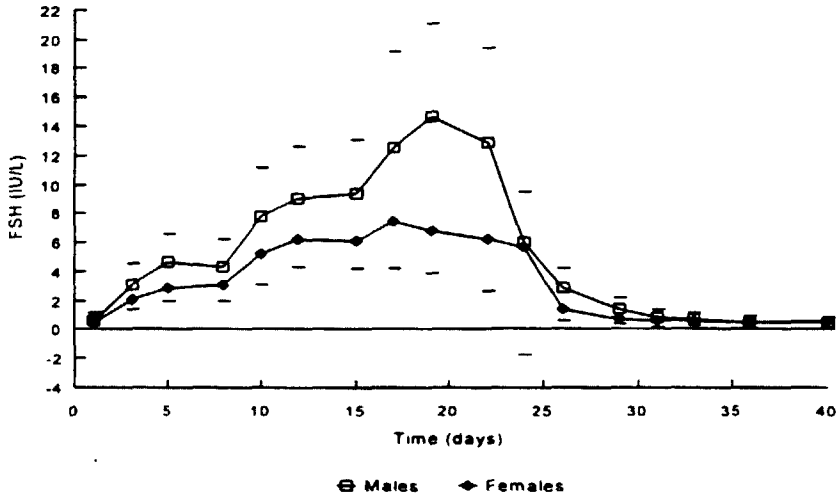

Table 28

	T½ (hrs)	p-value (males vs females)
Females	39 2 ± 7 9	0 02
Males	48 4 ± 5 4	

Pharmacodynamics

The efficacy of Org 32489 in facilitating follicle maturation in 7 gonadotropin deficient females is outlined in Table 29

Table 29

		FSH (IU/L)		Estradiol (pmol/ml)		Follicles	
Subject #	Diagnosis	Pre-level	Maximum level	Pre-level	Maximum level	Maximal Size (mm)	n
	hypophysectomy	0.07	8 32	7 6	112 1	11 - 13	1
	hypophysectomy	0 10	8 79	NA	18.0	<8	2
	hypophysectomy	<0 05	9 94	NA	48 5	None	0
	idiopathic	1 15	8 46	32 3	210 0	>17	3
	idiopathic	0 56	11 8	<5 1	76 7	>17	1
	idiopathic	1 07	10 1	37 7	139 5	>17	1
	idiopathic	0.25	7 13	11 1	42 6	14 - 16	1
Normal Range (follicular phase)		2 4 - 9 3		147 - 1470			

The range of serum hormones in gonadotropin deficient females pre-dose and after completion of each dose of Org 32489 (75. 150. 225 IU/day) are recorded in Table 30

Table 30

Day	LH (IU/L)	Progesterone (nmol/L)	Androstenedione (nmol/L)	Testosterone (nmol/L)
1	<0 05 - 0.37	<0 16 - 0.98	0 2 - 7 8	<0 38 - 0 69
8	<0 05 - 0.38	<0 16 - 0 88	0 14 - 3 26	<0 38 - 0 64
15	<0.05 - 0 13	<0 16 - 1 54	0 09 - 3 63	<0 38 - 0 51
22	<0 05 - 0 47	<0 16 - 1 56	0 15 - 4 14	<0 38 - 0 57
Normal Range (follicular phase)	1 6 - 9 3	0 3 - 4 8	1 4 - 15 7	0 2 - 3 0

Sponsor's Conclusions:

1 The T½ of rFSH in males is significantly longer than that in females

2 The multiple dose serum levels seem to be lower than the expected levels from a multiple dose simulation from single dose FSH levels (simulation data not shown)

3 Daily Org 32489 treatments to gonadotropin deficient females induced multiple follicular growth with only minor rises in serum estradiol levels and no effect on other serum hormones (LH, progesterone, androstenedione and testosterone).

Reviewer Comments:

1 A sex related difference in FSH T½ appears to exist However, since the indication sought in this submission is solely a female indication (development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology program and induction of ovulation and pregnancy in the anovulatory infertile patient with functional infertility) this finding has no clinical relevance at this time