

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21057

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

JUN 25 1999

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 21-057

Drug: Org 37462 (Ganirelix acetate) injection

Sponsor: Organon, Inc.

Dates of Submission: 01/28/99, 02/09/99, 05/07/99, 05/19/99, 06/07/99

Type of Submission: Original NDA (NME), 1P

Reviewer: Venkateswar R. Jarugula, Ph.D.

I. SYNOPSIS

The active ingredient in Org 37462 injection is ganirelix acetate, a gonadotropin releasing hormone (GnRH) antagonist, originally developed by [redacted]. It is a decapeptide derived from the native GnRH with substitutions of amino acids at positions 1, 2, 3, 6, 8, and 10. Org 37462 injection is indicated for the prevention of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian hyperstimulation. After initiating follicle stimulating hormone (FSH) therapy on Day 2 or 3 of the cycle, Org 37462 injection 250 µg may be administered subcutaneously once daily during the early to mid follicular phase. Treatment with ganirelix acetate should be continued daily until the day of human chorionic gonadotropin (hCG) administration. Org 37462 is supplied in a pre-filled 1 ml glass syringe containing 250 µg/0.5 ml of ganirelix acetate and is intended for subcutaneous administration only.

In the Human Pharmacokinetics and Bioavailability section of the NDA, a total of eight (8) studies were submitted. Out of these, five studies were conducted by Organon in Netherlands, and the rest were conducted by [redacted] under IND [redacted]. Organon studies included information on absolute bioavailability, bioequivalence, single dose, multiple dose pharmacokinetics, mass-balance and pharmacodynamic effects on gonadotropins. Organon claims that the studies conducted by [redacted] were not verified for accuracy and these studies were submitted only to satisfy full disclosure requirements and these results do not support any claims for this product. Therefore, [redacted] studies have not been evaluated in this review. A question based approach has been followed for the review of this NDA.

Ganirelix is rapidly absorbed into the systemic circulation following subcutaneous injection with an average T_{max} of 1 h and eliminated with a mean terminal half-life ranging 13 to 16 h. The pharmacokinetics of ganirelix are dose proportional in the dose

range of 0.125 mg to 0.5 mg. The absolute bioavailability of single dose 0.25 mg ganirelix following subcutaneous administration is 91%.

The mean volume of distribution of ganirelix in healthy human females following i.v. administration is 44 L indicating some tissue distribution. The *in vitro* plasma protein binding is 81.9% and is independent of plasma levels over 100 ng/ml – 10 µg/ml.

Following i.v. administration of radiolabeled ganirelix acetate, unchanged drug was the major radioactive compound present in plasma up to 4 h post-dose (50-70% of plasma radioactivity). Approximately 17-18% of the administered dose was excreted as unchanged drug in urine. The 1-4 peptide, 1-6 peptide and an unknown metabolite were the main metabolite fragments observed in feces. Approximately 22% of the total administered dose was excreted in urine within 24 hours and about 75% was excreted in feces.

From the dose ranging study, 0.25 mg was shown to be the optimal effective dose with effective decrease in number of premature LH surges and highest pregnancy rate.

Reviewer Comments

- The pharmacokinetics of ganirelix has not been evaluated in special populations such as hepatically and renally impaired patients. This may not be a concern because this is peptide drug, which is not likely to have any CYP450 metabolism, and is likely to be broken down by peptidases. Moreover, the patient population for the indication sought are relatively young and healthy.
- No specific drug-drug interaction studies were conducted for this application. Since this is a peptide drug, drug-drug interactions are not usually a concern.

II. RECOMMENDATION

NDA 21-057 for ganirelix acetate is acceptable from Clinical Pharmacology and Biopharmaceutics perspective. The sponsor should revise the Clinical Pharmacology section of the labeling as specified in the Labeling section of this review.

JS 6/25/99
Venkateswar R. Jarugula

FT signed by Ameeta Parekh, Ph.D., Team Leader _____

JS 6/25/99

Attendees at CPB briefing: Drs Lesko, Huang, Slaughter, M.Chen, Mehta, Lazor, Parekh, Lau, Madani, and Chatterjee

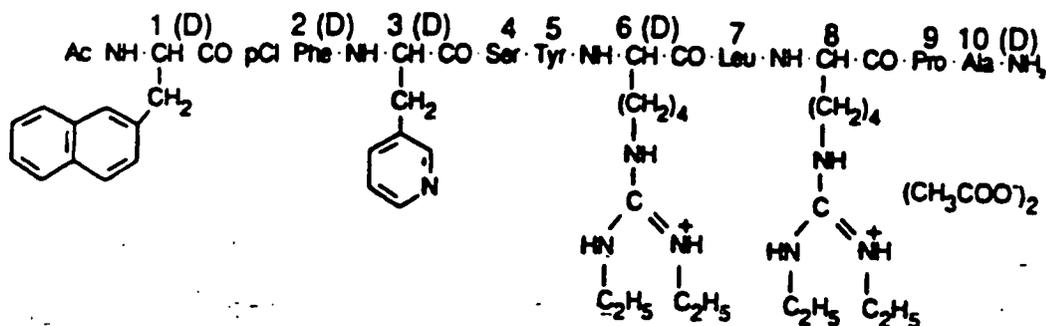
Cc: NDA 21-057, HFD-580 (Bennett, Moore), HFD-870 (M.Chen, Parekh, Jarugula), CDR(B.Murphy for Drug).

III. BACKGROUND

Women undergoing controlled ovarian hyperstimulation (COH) for assisted reproductive techniques (ART) without the addition of gonadotropin releasing hormone analogues, show LH rises, irrespective of the treatment schedule used. Usually, these rises occur prematurely, due to a positive feedback of rising estradiol (E_2) levels produced by a cohort of relative small follicles. The exposure of non-mature follicles to high levels of LH leads to premature luteinization of granulosa cells and hence to increased production of progesterone (p) and decreased synthesis of E_2 . These changes may cause disrupted maturation and decreased fertilization and implantation rates. Success rates of COH cycle in which premature LH rises are detected, are reported to be low. Often these cycles are cancelled because the number and/or size of follicles are still too small.

To avoid premature LH rises, GnRH agonists are currently used although none of these agonists have been approved by FDA for this indication. However, the use of GnRH agonists during COH is associated with disadvantages, such as initial flare-up of LH, the rather long period until pituitary suppression becomes effective, and possible higher dose of FSH required for COH with concomitant down regulation, due to suppression of endogenous FSH. In contrast GnRH antagonists suppress LH immediately following administration, by competitively blocking GnRH receptors.

Ganirelix acetate is a GnRH antagonist developed originally by Syntex Research (Palo Alto, CA). It is a decapeptide derived from GnRH with substitutions of amino-acids at positions 1, 2, 3, 6, 8, and 10 and the chemical structure is shown below. Ganirelix acetate has high aqueous solubility.



IV. CLINICAL PHARMACOLOGY

ADME (Study 38613):

Q. What is the fate (ADME) of the drug following intravascular administration?

The *in vivo* mass balance (metabolism and excretion) of ganirelix acetate was investigated in an open-label, single dose study (38613) following a single intravenous injection of 1 mg (25 μ Ci) ¹⁴C-labeled Org 37462 in three healthy female subjects. The results obtained in the study are summarized in Tables 1 and 2.

Table 1. Cumulative Fecal and Renal Excretion of [¹⁴C]-Radioactivity

Feces			Urine		
Collection Interval (h)	Mean (% of dose)	SD	Collection Interval (h)	Mean (% of dose)	SD
Pre-dose	0.0	0.0	Pre-dose	0.0	0.0
0 - 24	8.1	14.1	0 - 4	13.4	1.3
24 - 48	18.3	23.7	4 - 8	16.4	0.8
48 - 72	42.0	17.0	8 - 12	18.0	0.7
72 - 96	49.7	23.7	12 - 24	20.4	0.7
96 - 120	60.5	9.6	24 - 48	21.5	0.8
120 - 144	66.3	4.7	48 - 72	21.9	0.8
144 - 168	69.7	3.8	72 - 96	22.1	0.8
168 - 192	71.1	3.6	96 - 120	22.1	0.8
192 - 216	72.3	4.3	120 - 144	22.1	0.8
216 - 240	73.1	4.9	144 - 168	22.1	0.8
240 - 264	73.8	5.0	168 - 192	22.1	0.8
264 - 288	74.2	5.5			

Time intervals are limited to 288 h and 192 h for feces and urine, respectively, since only those intervals are included at which samples from all three subjects were available.

Table 2. Summary of Total Excretion of [¹⁴C]-Radioactivity

Parameters	Mean	SD	min. - max
A ^u _∞ (% of dose)	22.1	0.8	
A ^f _∞ (% of dose)	75.1	6.4	
A [∞] (% of dose)	97.2	5.6	

A^u_∞: total [¹⁴C] - radioactivity excreted in urine

A^f_∞: total [¹⁴C] - radioactivity excreted in feces

A[∞]: total excreted amount of [¹⁴C] - radioactivity

Summary statistics are presented for time interval 0-768 h for subject 0001, 0-336 h for subject 0002, and 0-288 h for subject 0003 (i.e. the time interval from dosing up to the last measurable feces sample).

Approximately 97% of the total administered dose was recovered through urine (22%) and feces (75%). Urinary excretion was virtually complete in 24 h, whereas fecal excretion continued until 192 h following drug administration.

Plasma levels of [¹⁴C]-radioactivity declined rapidly, reaching the limit of quantitation between 48 and 72 hours post administration. The mean apparent elimination half-life of plasma radioactivity was 10.4 hours.

Unchanged Org 37462 was the major radioactive compound present in plasma up to 4 hours post-dose (50-70%) and in urine (85%) whereas unchanged drug was not observed in feces. Approximately 18% of the dose was excreted unchanged in urine. Main metabolites observed in feces were: 1-4 tetrapeptide (20 to 30% of the dose in all subjects), 1-6 peptide (30% of the dose in one subject) and an unknown metabolite (20% of the dose in two subjects).

ABSOLUTE BIOAVAILABILITY

Q. What is the absolute bioavailability of the ganirelix acetate following subcutaneous injection and what are the pharmacokinetic characteristics following single dose administration?

An open-label, randomized, two-way crossover, single-dose study (38604) was conducted to assess the absolute bioavailability of 0.25 mg Org 37462 after single subcutaneous injection in 16 healthy young female subjects. Serum levels of Org 37462 in all subjects were above the limit of quantification until at least 48 hours post-dosing and serum levels were generally comparable between SC and IV administrations from 1.5 hours after dosing with similar elimination half-life. The mean plasma concentrations and pharmacokinetic parameters following IV and SC administration are listed in Fig 1 and Table 3, respectively.

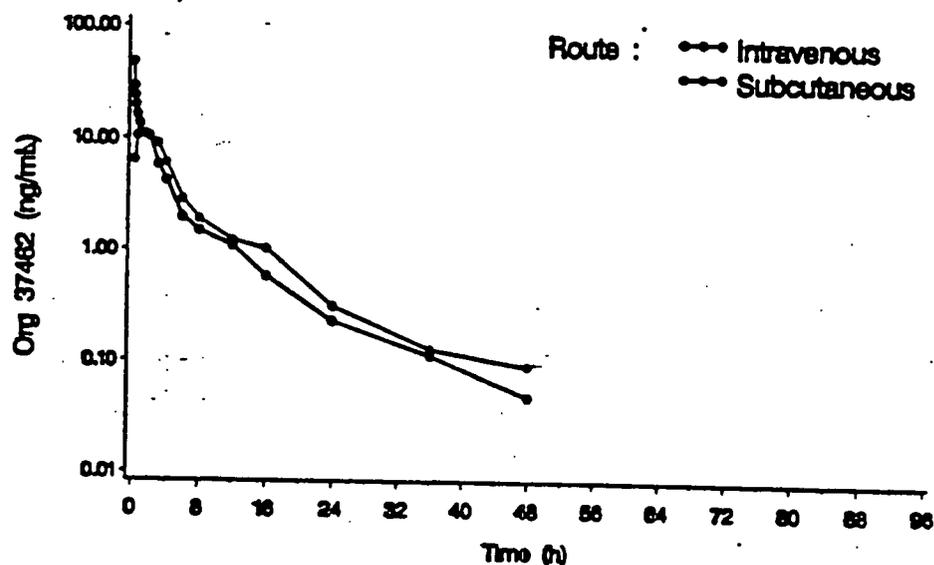


Figure 1. Mean logarithmic serum levels of ganirelix following single dose i.v. and sc administration of 0.25 mg ganirelix acetate.

Table 3. Mean \pm SD pharmacokinetic parameters following IV and SC administration 0.25 mg ORG37462

Parameter	IV	SC
F (%)	-	91.3 \pm 6.7
AUC ₀₋₂₄ (ng·h/ml)	103 \pm 10	94 \pm 11
AUC _{0-∞} (ng·h/ml)	105 \pm 11	96 \pm 12
C _{max} (ng/ml)	-	14.8 \pm 3.2
t _{max} (h)	-	1.1 \pm 0.3
t _{1/2} (h)	12.7 \pm 3.7	12.8 \pm 4.3
k _{el} (h ⁻¹)	0.039 \pm 0.017	0.060 \pm 0.019
CL (L/h)	2.4 \pm 0.2	-
V _d (L)	43.7 \pm 11.4	-

The mean absolute bioavailability of ganirelix was 91%. The mean systemic clearance (0.04 L/min) was found to be far less than the average hepatic blood flow (1.5 L/min) suggesting that this is a low clearance drug (low extraction ratio). The mean volume of distribution of ganirelix was 44 L, which is less than the total body water 57 L in a 70 kg adult but more than the blood volume and extracellular volume. This indicates that the drug also distributes into tissues to some extent. The inter-subject variability is low (12% for AUC and 22% for C_{max}) after subcutaneous administration.

DOSE-PROPORTIONALITY

Q. Is the pharmacokinetics dose proportional?

Study 38605 with an open-label, parallel design was conducted to assess the dose proportionality of ganirelix pharmacokinetics following multiple dose administration for seven days with once a day dosing. A total of 45 healthy female subjects (15 per dose level: 0.125, 0.25, and 0.5 mg) participated in this study. After a pill free period, with synchronized menstrual cycle, patients were randomized to treatment groups A (0.125 mg), B (0.25 mg) and C (0.5 mg). The mean pharmacokinetic parameters at steady state are summarized in Table 4.

Table 4. Mean Values (and SD) of the Pharmacokinetic Parameters

Parameter	Units	Dose = 0.125 mg (n = 15)	Dose = 0.25 mg (n = 15)	Dose = 0.5 mg (n = 15)
C_{max}	ng/mL	5.23 (0.80)	11.16 (2.41)	22.15 (3.43)
$Dn-C_{max}$	ng/mL	41.82 (6.41)	44.64 (9.65)	44.29 (6.86)
t_{max}	h	1.04 (0.47)	1.14 (0.23)	1.12 (0.40)
AUC_{0-24}	ng.h/mL	32.96 (4.20)	77.13 (9.75)	137.83 (17.02)
$Dn-AUC_{0-24}$	ng.h/mL	263.67 (33.57)	308.53 (39.01)	275.66 (34.03)
$t_{1/2}$	h	13.65 (3.36)	16.19 (1.64)	16.32 (1.03)
k_{el}	1/h	0.054 (0.013)	0.043 (0.005)	0.043 (0.003)
C_{tr}	ng/mL	1.37 (0.18)	3.21 (0.41)	5.74 (0.71)
Cl_{app}	L/h	3.85 (0.51)	3.29 (0.41)	3.69 (0.51)
V_{app}	L	74.91 (17.26)	76.53 (10.27)	86.59 (11.35)
$t_{1/2}^{\beta}$	days	4 (3-7)	4 (3-6)	4 (3-5)

Median and range tabulated instead of mean and SD

Dn- Dose normalized

The results summarized in the above table demonstrate that the pharmacokinetics of ganirelix are dose-proportional in the dose range of 0.125 to 0.5 mg, although the dose normalized AUC was higher at 0.250 mg dose. Steady-state was reached by Day 4 based on the trough levels of ganirelix. T_{max} and weight normalized Cl_{app} were dose independent. The half-life at the lowest dose group was significantly lower than that at higher dose groups. This is most likely due to the shorter time interval that was used for the estimation of terminal slope at 0.125 mg dose.

The inter-individual variability in C_{max} (22%) and AUC (13%) was low at the to be marketed dose, 0.25 mg. Similar variability was noted in the single dose absolute bioavailability study. From the trough levels measured, the drug does not seem to accumulate more than predicted from the half-life ($C_{min,day1}/C_{min,day2}$ for 0.25 mg = 1.29).

PHARMACODYNAMICS

Q. What is the effect of ganirelix on serum LH levels?

In the multiple dose study (38605), serum LH levels were measured at predose on days 1 to 7 and at 2, 4, 8, 12, 16, 24, 36, 48, 72 and 96 h after drug administration on day 7. The median serum LH levels are illustrated in Fig 2.

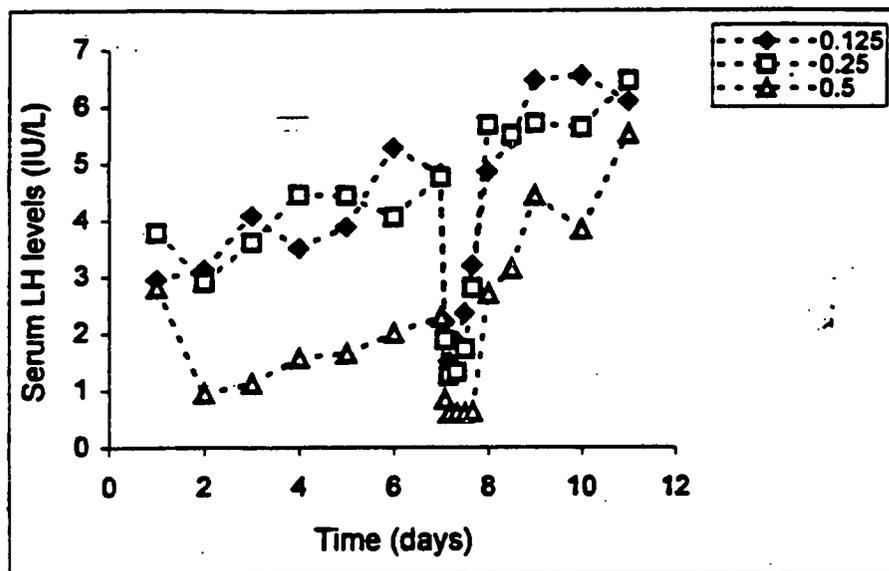


Fig.2. Median serum LH levels following multiple dose administration of ganirelix acetate for 7 days.

There was a clear drop in pre-dose serum LH levels following 0.5 mg injection, whereas with the two lower doses there was only a small decrease or no change from baseline. During daily treatment with ganirelix, pre-dose serum LH levels increased gradually (possibly due to changes in LH baseline during follicular phase of menstrual cycle). From the Day 7 data, it appeared that there was dose-related suppression of serum LH and the nadir LH levels were reached 4 hrs (median) after each dose level. But the suppression effect is more pronounced for the 0.5 mg dose compared to the lower doses. Twenty-four hour after the last injection, serum LH levels had returned to pre-dose values and increased further thereafter. Administration of ganirelix at these doses also caused reversible suppression of FSH and E_2 levels. The effect of ganirelix on serum thyroid stimulating hormone (TSH), growth hormone (GH) and prolactin was evaluated by measuring hormone levels in a subset of 25 subjects from the 0.25 mg dose group during and after treatment with recFSH and ganirelix. In general, the median serum levels of TSH and GH seemed to be unaffected by ganirelix 0.25 mg dose although there was transient raise in serum GH levels on day 3 of ganirelix dosing. From the first day of ganirelix treatment onwards, the median serum prolactin levels gradually increased up to and above the upper reference value (14.6 ng/ml) and the prolactin levels remained increased after treatment with ganirelix up to the second week after ET. According to the sponsor's explanation, the increase in prolactin levels could be due to the increasing concentrations of serum estradiol.

Sponsor did not attempt to explore the PK/PD relationship between serum levels of ganirelix and the degree of suppression of LH. However, it may be complicated to develop a physiologically plausible PK/PD model because of complex feedback mechanisms involved in the pulsatile release of endogenous LH baseline levels. Additionally, baseline LH levels were not measured at multiple time points to allow modeling of the baseline. Any PK/PD model developed should take into account

pulsatile release of LH and the differences in early and mid follicular phases of menstrual cycle. Furthermore, the model developed in normal volunteers may not apply to the patient population who will also receive COH therapy with recFSH (recombinant FSH) because of added complexities due to hyperstimulation of ovaries.

DOSE-RESPONSE

How does the response relate to escalating doses?

Is there a relationship between serum levels of ganirelix and the suppression of LH levels?

Is the dose selected for the pivotal trials appropriate?

Sponsor conducted a phase II, multi-center, double-blind, randomized, dose-finding study (38602) to select minimum effective dose of ganirelix acetate. One of six doses (0.0625mg, 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 2 mg) was administered once a day subcutaneously in women undergoing COH with recFSH. Selection of the optimal effective dose was based upon the efficacy of ganirelix in preventing premature LH surges, clinical outcome (number of oocytes and embryos, implantation rate and vital pregnancy rate) and the safety and tolerance of drug product.

The subjects in the study received one treatment cycle only. For COH, recFSH treatment (one daily SC injection) was started on Day 2 of the menstrual cycle (treatment day -5). After five days of recFSH treatment (=treatment day 1), ganirelix treatment was started by daily SC administration. During ganirelix treatment, the dose of recFSH was adjusted depending on the individual ovarian response by daily ultrasonography (USS). The treatment with ganirelix and recFSH were to continue until 3 follicles \geq 17 mm (assessed by USS) were present. On that same day, human chorionic gonadotropin (hCG) was to be given to induce ovulation and 30 to 36 h thereafter, oocyte pick-up was to be performed. Fertilization was to be performed by means of in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI). At embryo transfer, no more than three embryos were to be replaced. All subjects were to receive progesterone (P) or hCG as luteal phase support. In case of a premature LH surge ($LH \geq 15$ IU/L according to local laboratory immunoassay) during ganirelix treatment, the investigator was allowed to either cancel or rescue the cycle by giving hCG.

Blood samples to determine hormone levels and ganirelix levels were taken just prior to ganirelix acetate injection (a.m. time points) and approximately 8 h later (p.m. time points). The mean serum levels of ganirelix and LH are depicted in Fig 3.

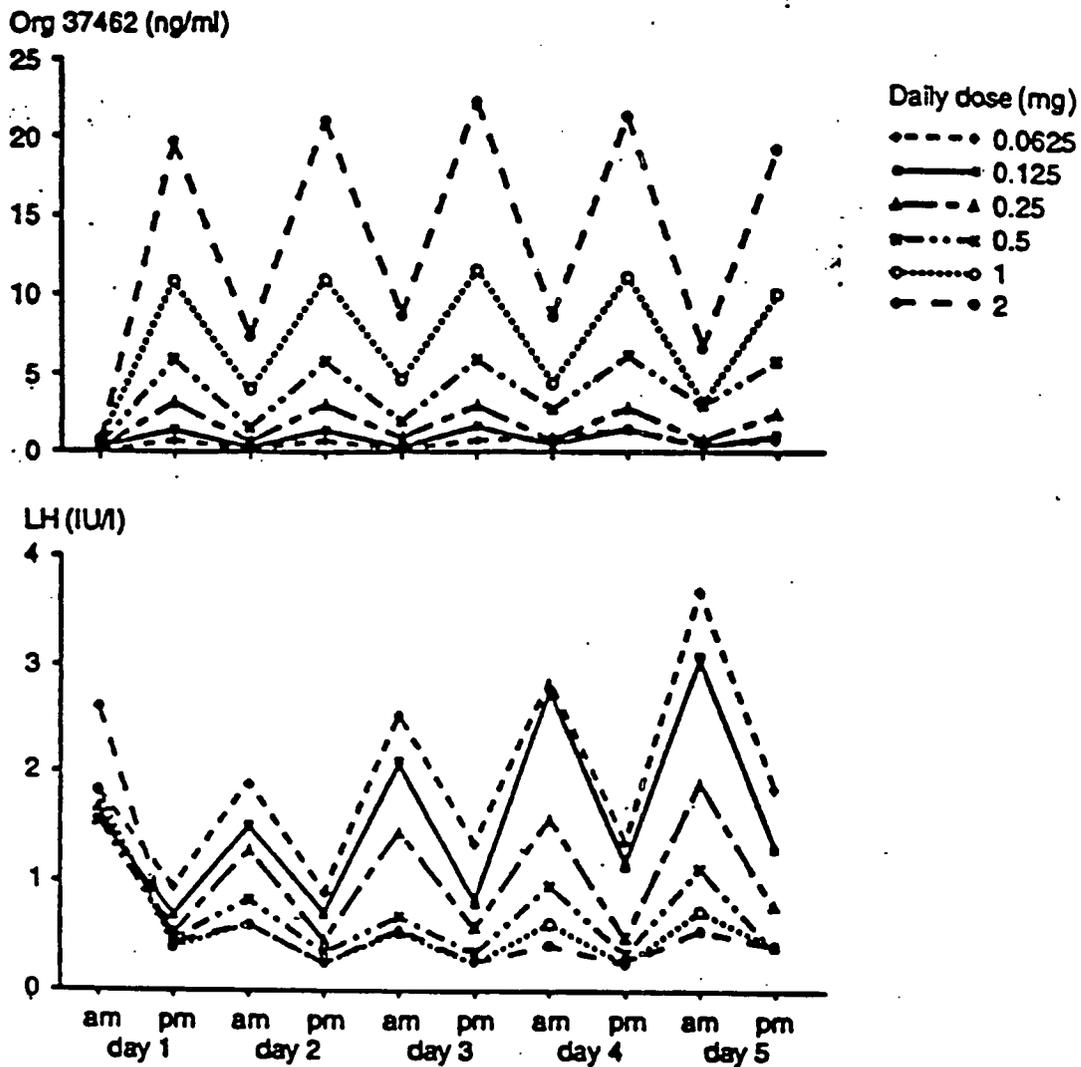


Figure 3. Serum ganirelix (upper panel) and LH (lower panel) levels measured just before each ganirelix acetate injection in the morning (am) and measured at 8 h later in the afternoon (pm).

There was dose proportional increase in serum ganirelix levels. The suppression of LH was dose dependent. The LH suppression is reversible within 24 hours following drug administration at lower doses. Higher doses caused greater suppression of LH with less readily reversible suppression of LH. Predose serum LH levels gradually increased at lower doses. This may be due to increased estradiol levels in late follicular phase which result in increased GnRH secretion, which in turn causes displacement of ganirelix at the receptor level. No PK/PD analysis was performed in this study (refer to the discussion in Pharmacodynamics section of the review).

Table 5. Results from the multicenter, double-blind, randomized, dose-finding study to assess the efficacy of Org 37462 to prevent premature LH surges in women undergoing COH with recombinant FSH.

Daily dose (μg) of Org 37462

	62.5 μg	125 μg	250 μg	500 μg	1,000 μg	2,000 μg
No. subjects receiving Org 37462	31	66	70	69	66	30
No. subjects with ET [†]	27	61	62	54	51	27
LH rise ≥ 10 mIU/mL [‡]	5	6	1	0	0	0
Serum LH (mIU/mL) on day of hCG [§]	3.6	2.5	1.7	1.0	0.6	0.3
Serum E ₂ (pg/mL) on day of hCG [§]	1475	1110	1160	823	703	441
5 th -95 th percentiles	645-3720	424-3780	384-3910	279-2720	284-2360	166-1940
No. of follicles ≥ 11 mm [¶]	10.7(5.1)	10.7(4.8)	11.8(4.6)	10.1(4.7)	10.8(4.7)	10.2(5.2)
No. of oocytes [¶]	8.7(5.8)	9.6(5.4)	9.8(5.5)	8.8(6.6)	9.4(6.2)	9.1(5.3)
No. of embryos [¶]	5.2(3.6)	5.8(4.3)	5.2(4.5)	4.6(4.2)	5.5(4.4)	5.6(4.6)
No. of embryos transferred [¶]	2.7(0.9)	2.6(1.0)	2.4(0.9)	2.3(0.6)	2.4(0.8)	2.6(1.0)
Vital pregnancy rate [¶]						
per attempt, n (%)	7(22.6)	17(25.8)	25(35.7)	8(11.6)	9(13.6)	2(6.7)
per transfer, n (%)	7(25.9)	17(27.9)	25(40.3)	8(14.8)	9(14.8)	2(7.4)
Implantation rate (%) [¶]	14.2(26.8)	16.3(30.5)	21.9(30.6)	9.0(23.7)	8.5(21.7)	4.9(20.1)

* Number of subjects with LH rises following initiation of Org 37462 therapy. Includes subjects who have complied with daily injections.

‡ Median values

§ Restricted to subjects with hCG injection

¶ Mean (standard deviation)

† ET: Embryo Transfer

¶ As evidenced by ultrasound at 5-6 weeks following ET.

The results of this study showed that the incidence of LH rises ≥ 10 IU/L were dose dependent i.e., as the dose increased, the LH rises decreased. The suppression of serum LH levels was clearly dose related with median serum LH levels on the day of hCG administration ranging from 3.6 IU/L in the 0.0625 mg group to 0.35 IU/L in the 2 mg group. The dose-response relationship was also evident from the serum ganirelix and LH levels measured at predose and 8hrs after each dosing as illustrated in Fig 3 above.

A statistical subset selection procedure was used to select the dose group with the best effect. The procedure was defined such that with 95% confidence the selected subset of dose groups contained the true best dose group. The dose selection procedure using the above mentioned statistical method was applied to the number of follicles, number of oocytes, number of good quality embryos and the vital pregnancy rate. Based on this procedure, 0.25 mg dose that resulted in highest pregnancy rate and implantation rate

with sufficient LH suppression was selected as the optimal effective dose for further phase III studies.

Although there were no rises >10 IU/L at 0.5, 1 and 2 mg doses, the vital pregnancy rates and implantation rates were lower at these doses compared to 0.25 mg dose. Sponsor did not give any explanation for this result. However, based on discussion with medical review team, it appears that serum LH levels were suppressed too much at these dose levels and also the estradiol levels were also too low to result in good quality embryos and implantation rates.

Population pharmacokinetic analysis was performed on sparse sampling data for ganirelix. A one compartment first-order absorption model was used to describe the serum concentration Vs time data. Population parameters for CL, VD and KA, inter-individual variability and intra-individual variability in these parameters were estimated using NONMEM analysis. The effect of covariates such as age, height, body weight and body mass on CL and VD was examined. The population PK parameter estimates from NONMEM analysis are listed in Table 6.

Table 6. Pharmacokinetic Population Parameter Estimates According to the One-Compartment Model with First-Order Absorption

	value	Standard Error	Inter-individual variability (%)
CL (L/hr)	4.82	0.129	16
V _d (L)	68.5	3.54	24
K _{abs} (h ⁻¹)*	2.81	4.57	213
t _{1/2α} (h)	9.85	n.a.	n.a.

*Absorption half-life of 0.247 h.

As can be noted from the table, the inter-individual variability in CL and VD are similar to those observed in other PK studies, whereas absorption rate constant is associated with high variability because of lack of data in the absorption phase. Sponsor did not report any intra-individual variability because the initial estimate of variance of intra-individual variability (denoted by 'SIGMA' in NONMEM) was fixed as one. The reason for fixing the intra-individual variability in the analysis has not been explained in the submission. The NONMEM data analysis showed no influence of the covariates on CL and VD. However, it should be noted that the covariates ranges are narrow (age: 32±4 years, weight: 62.3±7.9 kg, and lean body mass: 45.4±4.6). Trough levels of ganirelix showed that steady-state has been reached by two days of treatment and the pharmacokinetic is linear between dose range of 0.0625 mg to 2 mg.

The serum concentrations of ganirelix on the day of OPU were significantly linearly correlated with the concentration in the follicular fluid.

The drug related adverse events reported during the treatment include ovarian hyperstimulation syndrome, abdominal pain (gynecological), nausea, fatigue, malaise and application site reactions. The percentage of subjects with a moderate to severe local

tolerance reaction 1 hour after injection of any dose was 21.7% (moderate=20.5%, severe=1.2%) and at 24 hour after the injection only 4.2% of the subjects reported a reaction. Among the skin reactions reported, redness (19.6%) was the most commonly reported adverse event. The incidence of skin redness and swelling appear to be related to dose, with higher incidences at higher dose groups.

SPECIAL POPULATIONS

Q. How is the disposition of Ganirelix altered in special populations?

Q. How important is the special populations information for the given indication?

The pharmacokinetics, safety and efficacy of ganirelix have not been studied in elderly, renally and hepatically impaired patients.

Lack of PK information in special populations may not be a concern because of following reasons:

- Ganirelix is a peptide, which is not likely to be metabolized by CYP450 enzymes.
- Only 18% of the dose is excreted unchanged in the urine.
- The patient population for the given indication is relatively young and healthy.

DRUG-DRUG INTERACTION

Q. Does this drug interact with any other drugs?

No specific Drug-Drug interaction studies were conducted with ganirelix. However, the sponsor appropriately stated in the labeling that since ganirelix can suppress the secretion of pituitary gonadotropins, dose adjustments of exogenous gonadotropins might be necessary when used during COH.

VI. BIOPHARMACEUTICS

FORMULATION

Q. What are the changes between the clinical trials formulation and the commercial formulation?

Q. How is the commercial formulation linked to clinical trials formulation?

The qualitative and quantitative composition and the manufacturing process are essentially the same for the clinical batches and the to be marketed product. In contrast to the marketed product, all clinical batches were filled in 2 ml vials (0.5 ml extractable volume per vial). Another difference was that hydrochloric acid was used to adjust the pH in clinical batch CP 097106 (this was used in study 38608) as opposed to the use of acetic acid in the to be marketed product.

Table 7. Formulations Used in Org 37462 Studies Conducted by Organon

Batch number	CP 096030	CP 096019	CP 096020
Dosage form	Solution for injection	Solution for injection	Solution for injection
Formulation			
-Org 37462*	0.125 mg/mL	0.25 mg/mL	0.5 mg/mL
-Mannitol	47.0 mg/mL	47.0 mg/mL	47.0 mg/mL
-Glacial Acetic Acid	0.4 mg/mL**	0.2 mg/mL	0.2 mg/mL
-Sodium hydroxide 1M	to pH 5.0	to pH 5.0	to pH 5.0
-Water for Injection	to 1.0 mL	to 1.0 mL	to 1.0 mL
Batch size	1500 mL	1500 mL	1500 mL
Content			
Assay Test Results	102 (%)	103 (%)	104 (%)

* Org 37462 is expressed as free base

** A higher amount of Glacial Acetic Acid was used to correct for lower buffer capacity at low concentrations of Org 37462.

Since there was no difference in the qualitative and quantitative compositions between the clinical trials and the to be marketed formulation with the exception of the above noted minor differences, no bioequivalence study was necessary.

BIOEQUIVALENCE

Sponsor conducted a multiple dose study to assess the bioequivalence and local skin reaction after SC administration of Org 37462 by Medi-jector® compared to a conventional needle injection. Apparently, the sponsor anticipates the use of this drug for the long-term treatment of gynecological disorders. Therefore, an easy-to-use, needle-free administration method is preferred. For diabetic patients the Medi-jector® has become available for insulin administrations. Medi-jector® is a needle-free delivery system that uses pressure to penetrate the skin and disperse the medication into the subcutaneous tissue.

Table 8. Bioequivalence Summary

Parameter	Units	Conv. needle (reference)	Medi-jector® (test)	Point Estimate ¹	90% Confid. Interval
C _{max}	ng/mL	91.29	93.56	1.02	0.97-1.08
t _{max}	h	0.98 ²	1.47 ²	0.50	0.13-0.88
AUC ₀₋₂₄	ng.h/mL	770.20	787.16	1.02	0.97-1.08
C _{tr}	ng/mL	32.15	32.85	1.02	0.97-1.08
C _{min}	ng/mL	10.13	9.50	0.94	0.87-1.02

¹ ratio /Conv. needle"; for t_{max} difference "Medi-jector®-Conv. needle"

² arithmetic mean

The pharmacokinetics of ganirelix was bioequivalent following the administration by and conventional needle methods. Steady-state serum levels were reached by

day 3 of the administration as evidenced by the trough levels. Serum concentrations of LH and E₂ were below the limit of quantification from approximately Day 2 onwards. No difference in local tolerance was observed between the subcutaneous administration by Medi-jector or by conventional needle.

Since the present indication is short-term, this method is not proposed in the labeling of this application. Therefore, the BE study is not relevant for this NDA.

ANALYTICAL METHODOLOGY

VII. LABELING

The Clinical Pharmacology section of the labeling should be revised by incorporating the highlighted changes as shown below.

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