CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21057

MEDICAL REVIEW(S)

JUN 16 1999

Medical Team Leader Secondary Review
Ganirelix Acetate

NDA:	**21-057**
Drug:	**Ganirelix acetate**
Dosage Form/Route:	**250 µg/0.5ml extractable volume of sterile, isotonic aqueous solution in 1ml glass pre-filled syringe. Administered via subcutaneous injection once daily during the early to mid follicular phase of a stimulation cycle and continued until the day of hCG administration.**
Applicant:	**Organon, Inc**
Original Submission date:	**January 28, 1999**
Review Completed:	**June 14, 1999**
Date of Memorandum:	**June 15, 1999**

Background

The medical discipline of infertility is a rapidly evolving highly technical field that has quickly embraced many new techniques and products. Not uncommonly, many of these techniques and products have come to be accepted as "Standard of Care" without the kinds of rigorous placebo-controlled studies that are generally desired by this regulatory agency particularly in the drug approval process. Such is the case for the use of GnRH analogs (specifically GnRH agonist) as adjunctive therapy in IVF protocols to reduce the incidence of premature luteinizing hormone (LH) surges and luteinization.

Although the first successful IVF attempts resulted from a single oocyte retrieved from a spontaneous menstrual cycle and use of natural cycle IVF has received renewed interest, most IVF cycles are performed after controlled ovarian hyperstimulation with gonadotropins. The use of gonadotropins either alone or in combination with clomiphene citrate for controlled ovarian hyperstimulation necessitates close monitoring of ovarian follicular development. In spite of such close monitoring, historically upwards to 30% of patients receiving these regimens had a premature surge of luteinizing hormone (LH) resulting in cycle cancellations (no retrieval). A premature LH surge occurring before follicles are sufficiently mature may disrupt the final stages of follicular maturation and have a negative impact on the quality of the oocyte. Poor quality oocytes lead to lower rates of fertilization and conception. Since the late 1980s, GnRH agonists have been used in the United States "off-label" for the indication of reduction in premature LH surge and subsequent improvement in the cycle cancellation rate. The use of GnRH agonists in Assisted Reproductive Techniques (ART) programs has increased from 41% of all ART clinics in 1988 to currently 97% or greater of all ART clinics as reported by the United States IVF Registry, a collaborative effort by the Society of Assisted Reproductive Technology (SART) of the American Fertility Society and Medical Research International. In 1988 of 2, 623 Embryo Transfer (ET) cycles recorded through RecordKeeper (a PC-based data recording system designed for ART clinics), 31% of IVF cycles utilizing stimulation with human menopausal gonadotropin (hMG) alone were cancelled while 32% of the cycles utilizing stimulation with the combination of hMG and FSH were cancelled. When GnRH agonists were added to these regimens, cancellation rates dropped to 18% and 23%, respectively for hMG and hMG plus FSH protocols. The clinical pregnancy rate of 21% expressed per embryo transfer for the combination of hMG, FSH and GnRH agonist was greater than the pregnancy rate in regimens not utilizing an agonist. The corresponding pregnancy rate without agonists was 13%. In 1989, ART clinics reported performing 18,211 stimulation cycles for IVF, 15,392 (85%) of which resulted in retrievals. ET (13, 523) resulted from 88% of the retrievals. Seventy-three (73%) percent of the clinics reported administering a GnRH agonist. Of 3,465 ET cycles reported to RecordKeeper, the pregnancy and delivery rates were highest for the regimens that included a GnRH agonist. The clinical pregnancy rate was 21% for those with a GnRH agonist in the stimulation regimen compared to 17% without. The corresponding cancellation rates were 12.5% with GnRH agonist and 25% without. By 1990, 97% of the clinics reported administering a GnRH agonist as part of their most commonly used stimulation regimens. There were 4,930 stimulation cycles reported to

RecordKeeper that resulted in 4,044 retrievals and 3,405 embryo transfers. The clinical pregnancy rate per ET was 21% for stimulation regimens with GnRH agonist and 19% for regimens without. The corresponding cycle cancellation rates were 14% with a GnRH agonist and 27% without. From 1990 through 1995 (the most recent year for which SART data on ART clinics is published), GnRH agonist use has been maintained at about 97% of the clinics and the cancellation rate has been maintained at about 14%. In 1995 the clinical pregnancy rate for IVF was 23.7% per initiated cycle and 30.7% per embryo transfer. Although, the SART reports do not specifically indicate the reason for cycle cancellations, it is assumed that the majority were for premature luteinization with immature eggs. No GnRH analogs, agonist or antagonist, are currently approved in the United States for the indication of a reduction in the incidence of endogenous LH surge and subsequent luteinization in ART.

Organon is the first company to seek approval of a GnRH antagonist, ganirelix, in this country for the prevention of premature luteinization in ART. A pre-NDA meeting between Organon and the FDA was held in September of 1998. At that time it was agreed that Organon could submit their European conducted Phase III trial and a Phase II dose finding study as the pivotal trials for their NDA. The Sponsor presented the argument that a non-placebo-controlled trial was necessary because it would be unethical to have women receive less than the standard of care for their IVF procedure and that it would be difficult to recruit patients into a placebo-controlled trial. The Agency accepted the Sponsor's argument and an active comparator trial was accepted for the Phase III study. No agonist is approved in this country for this indication. Therefore, an approved drug could not be chosen as an active comparator. A decision was made to allow the Sponsor to compare ganirelix to a historical control. The Sponsor was to submit historical data to support the success rates in IVF without the use of an antagonist. A non-approved GnRH agonist was included in the Phase III trial as a reference. Buserelin was the GnRH agonist chosen as the reference. Buserelin is registered in 6 countries around the world for the indication of prevention of premature LH surges in ART. Three controlled clinical trials are submitted to support the efficacy and safety of ganirelix acetate for the prevention of premature endogenous LH surges in women undergoing controlled ovarian hyperstimulation (COH). The objectives and the results of these trials are summarized below.

Review of the Clinical Studies

Study 38602

Study 38602 was a Phase II double-blind, randomized, dose-finding study conducted in 13 centers and designed to select the minimal effective dose of ganirelix in preventing premature surges of endogenous LH in women undergoing COH with recombinant follicle stimulating hormone (rhFSH). A secondary objective was to show that ganirelix acetate was safe and well tolerated with respect to local reactions at the site of injection. 342 subjects were randomized to receive one of six doses of ganirelix acetate (2 mg, 1 mg, 0.5 mg, 0.25 mg, 0.125 mg and 0.0625 mg). The ganirelix dose was administered once daily subcutaneously in the abdominal wall around the umbilicus beginning after 5 days of recombinant FSH (recFSH) treatment. During ganirelix treatment, the dose of recFSH could be adjusted depending on the individual ovarian response as assessed by ultrasound. Human chorionic gonadotropin (hCG), 10,000 IU, was administered when at least 3 follicles ≥ 17mm were observed by ultrasound. Oocyte retrieval was performed 30 to 36h later. Fertilization was established by IVF with or without intracytoplasmic sperm injection (ICSI). Embryo transfer was performed with a maximum of three embryos replaced. All subjects received luteal phase support in the form of progesterone (intramuscular or intravaginal) or hCG. In the case of a premature LH rise (LH≥ 15 IU/L according to LH immunoassay), the investigator was allowed to either cancel or rescue the cycle by giving hCG, even thought the criteria for hCG administration had not been reached.

According to the protocol, an External Independent Advisory Committee was appointed in order to advise on stopping a treatment arm in case of a high incidence of LH rises during study treatment. During the study, some investigators informed Organon about one or more cases of extremely low serum LH and falling estradiol concentrations as well as follicular growth arrest after starting ganirelix treatment. The External Independent Advisory Committee was requested to review all available clinical data, in order to evaluate whether these observations were dose-related and whether, in their opinion, there was reason to stop one or more treatment arms. The Advisory Committee reviewed all rises of LH (≥15 IU/l according to the LH immunoassay of the local laboratory and ≥ 10 IU/L according to the LH immunoassay of the central laboratory). The Committee advised Organon to stop the highest (2 mg) and lowest (0.0625 mg) treatment dose. The discontinuation of the two treatment arms did not interfere with the selection of the minimal effective dose.

The selection of the minimal effective dose was primarily based on the number of subjects with LH rise ≥10 IU/L during treatment as analyzed at the central laboratory and the number of follicles, number of oocytes, number of good quality embryos and the vital pregnancy rate (see Table 1)

Table 1. Efficacy Parameters Used in the Dose Selection Procedure for Study 38602
Intent to Treat (ITT) Group
(Sponsor's Table 33 ESE)

Efficacy Parameter	Treatment Group					
	0.0625 N=31	0.125 N=65	0.25 N=69	0.5 N=69	1.0 N=65	2.0 N=30.
No. of subjects with an LH rise (≥10 IU/L)	5	7	2	0	1	0
Vital pregnancy rates, "per attempt"	N=31 7(22%)	N=66 17 (25.8%)	N=70 25 (35.7%)	N=69 8 (11.6%)	N=66 9 (13.6%)	N=30 2 (6.7%)
Number of follicles > 17mmon the day of hCG	N=31 4.0	N=66 4.6	N=70 4.5	N=69 4.0	N=66 4.4	N=30 4.3
Median number of cumulus-oocyte complexes	N=31 7	N=65[b] 8	N=70 9	N=69 9	N=66 8	N=30 8
Mean (SD), number of good quality embryos[a], "per attempt"	N=31 3.7 (2.80)	N=66 3.3 (2.62)	N=70 3.2 (2.98)	N=69 2.5 (2.69)	N=66 3.5 (3.4)	N=30 3.7 (3.80)

[a] Embryos of grade 1 (excellent) and 2 (good)
[b] Subject 0192 underwent oocyte retrieval but no oocytes were recovered

The 0.125 mg and the 0.25 mg were selected based on the vital pregnancy rates, number of follicles > 17 mm, median number of cumulus-oocyte complexes and mean number of good quality embryos. However, the 0.125 mg dose was eliminated because it had a higher number of subjects with LH surges.

No subjects discontinued the study because of an adverse event. A total of 16% of subjects experienced at least one adverse event. This is not an unusually high number. The most serious adverse event occurring was moderate ovarian hyperstimulation that occurred in two subjects in the 0.25 mg group. Ovarian hyperstimulation is a known effect of FSH administration and it is therefore unlikely that this effect is directly attributable to the administration of ganirelix acetate. Moderate to severe redness at the injection site of ganirelix occurred in 19.6% of subjects on ganirelix one hour after injection. By 24 hours postinjection this reaction was reduced to moderate severity and was found in only 1.2% of subjects.

Therefore, the 0.25 mg dose was determined to be the minimal effective dose and it was shown to be safe and well tolerated. The selection of the 0.25 mg dose appears to be valid and appropriate

The cancellation rate of 4.3 % in the 0.25 mg dosage group compares very favorably with the historical 14% cancellation rate with GnRH agonist as reported to the IVF registry in 1990, 1992, 1993, 1994 and 1995. The vital pregnancy rate per attempt of 35.7 % in the 0.25 mg dose exceeds that of 23.7 % per attempt reported in the last year that the SART IVF registry data has been published, 1995.

Study 38603

This study was a follow-up of pregnancies that occurred in subjects participating in study 38602. A total of 68 vital intrauterine pregnancies occurred in study 38602. There were 52 singleton, 11 twin and 5 triplets. Pregnancy outcome data was collected for 67 subjects. Of those subjects with follow-up data, six abortions occurred before 16 weeks gestation. Of 25 pregnant patients in the selected 0.25-mg dose group, two abortions occurred. Karyotyping of the abortus in one abortion identified Trisomy 18 (Edwards Syndrome). Of the 61 subjects with an ongoing pregnancy who had follow-up data, two subjects with singleton pregnancies did not give birth to a live-born infant. One subject aborted in week 19 and one subject had a fetal death in utero in week 27. Of the five initial triplet pregnancies, 4 triplets were reduced to twins by selective or spontaneous reduction. Of the 11 twins, 2 twins spontaneously reduced to singletons. Seventy-three infants, 33 boys and 40 girls, were born. Physical abnormalities were noted at birth in 9 babies, 8 diverse minor abnormalities and 1 major abnormality (Bechwith Wiedemann Syndrome characterized by exomphalos and macroglossia). These are small numbers but they suggest that ganirelix appears to be safe for the offspring of subjects treated with ganirelix.

Study 38607

Study 38607 was the pivotal study to demonstrate the efficacy and safety of ganirelix in women undergoing controlled ovarian hyperstimulation. It was a Phase III multi-center, open-label randomized study using buserelin as a reference treatment. The randomization was stratified by age, IVF with ICSI vs. IVF without ICSI, and primary vs. secondary infertility. A total of 486 subjects were randomized to 0.25mg ganirelix and 244 subjects to the buserelin group. The study was designed as a non-inferiority study.

Subjects in the ganirelix treatment group received recFSH (150 IU) by SC injection once daily starting on the 2nd or 3rd cycle day (treatment day1). Ganirelix (0.25mg) administered by SC injection once daily was started on treatment day 6. From treatment day 6 on, the dose of recFSH could be adjusted according to individual ovarian response. Treatment with recFSH and ganirelix was continued up to and including the day of hCG administration.

Subjects in the buserelin group began treatment between cycle day 21 and 24 (treatment day 1) of the previous menstrual cycle after a hCG test was performed to exclude pregnancy. Buserelin was administered intranasally with one puff (0.15 mg) administered four times per day. RecFSH (150 IU) was begun when a downregulated hypogonadotropic state (defined as estradiol < 50pg/ml) was reached. The dose of buserelin was increased to 1.2 mg daily, if down regulation was not achieved after 14 days of buserelin treatment. Any subject who had not achieved down regulation within 4 weeks of treatment, had treatment discontinued. The recFSH dose could be adjusted after 6 days of recFSH treatment depending on the individual ovarian response. Buserelin and recFSH were continued up to and including the day of hCG administration.

For both treatment groups hCG was administered on the day of treatment in which at least 3 follicles ≥ 17mm were measured by ultrasound. Oocyte retrieval was performed 30-36 hours after hCG administration. IVF with or without ICSI was performed and embryo transfer was done 2 to 5 days after oocyte retrieval. Embryo transfer was limited to replacement of a maximum of 3 embryos. Luteal phase support with progesterone was given according to the investigator's routine practice and was given daily for 2 weeks or until menses. Each subject was treated for only one IVF cycle.

The primary efficacy endpoints were the number of cumulus-oocyte complexes and the ongoing pregnancy rates. Considerations for the statistical analysis of these endpoints were as follows. The main aim of the study was to demonstrate that the mean number of cumulus-oocyte complexes and the ongoing pregnancy rate for ganirelix are not less than those obtained with the "current standard of care" to a clinically relevant degree. Assuming equal efficacy in both groups, a standard deviation (SD) of 6.4 for oocytes and an anticipated pregnancy rate of 20%, the standard error of the mean (precision) was calculated as 0.3 for the number of oocytes and 2.0% for the rate of pregnancy. Under these assumptions, the resulting lower limits for the 97.5% confidence intervals of the differences between ganirelix and the reference group were -1.1 oocytes and –7% for the pregnancy rates.

With respect to oocytes, a mean treatment difference of up to 3 oocytes between ganirelix and "current standard of care" was considered clinically acceptable. The outcome of an earlier recFSH study with a long protocol had shown a mean difference of 11 oocytes. Assuming that Ganirelix and the reference treatment have 'in reality' equal efficacy, the probability of finding that the upper 97.5% confidence interval for the difference between ganirelix and the reference treatment did not include –3 was over 99%.

For the pregnancy analysis, it was hypothesized that the pregnancy rate observed for IVF using ganirelix should be no more than 5% below the rate observed in the reference group. An earlier study had shown a pregnancy rate of 22% with the long protocol. If 'in reality' both treatments have equal efficacy, there was still approximately a 7% chance that the point estimate for the pregnancy rate in the ganirelix group would be 5% or more below the outcome in the reference group. The probability that the 97.5 confidence interval for the difference would exclude –5 % was only 30%. In other words, ganirelix would have to have had a significantly higher pregnancy rate than the control in order for the 97.5 % confidence interval to exclude –5%. Therefore, the Sponsor states that the confidence interval for the pregnancy rate was used as a measure of the precision of the trial only.

The results of the primary efficacy analysis are shown in Table 2 for the ITT group.

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Table 2
Statistical Analysis of the Number of Cumulus-oocyte complexes and Ongoing Pregnancy Rate for the Intent to Treat Group (N=70)
From Sponsor's Tables 20 and 21 volume 56

	Treatment Group		
	Ganirelix	Buserelin	Estimated treatment difference[a] Ganirelix minus Buserelin Lower bound of one-sided 97.5 % confidence interval
Number of cumulus-oocyte complexes	(N=463)	(N=238)	
Per Attempt			
Mean (SD)	8.7 (5.6)	9.7 (6.2)	N/A
Estimated treatment mean[a]	8.3	9.3	-1.0 (-1.8)
Per Retrieval[b]	9.1 (5.4)	10.4 (5.8)	N/A
Ongoing Pregnancies	(N=463)	(N=237)	
Per Attempt			
n (%)	94 (20.3%)	61 (25.7%)	N/A
Estimated treatment rate[a]	20.3%	25.7%	-5.4% (-11.9%)
Per Embryo Transfer[c]	(N=339)	(N=207)[d]	
n (%)	93 (23.3)	60 (29.0)[e]	N/A

[a] Adjusted for center using the Cochran-Mantel Haenszel approach; the adjustment treatment rate is a weighted average over the centers and is therefore different from the raw (unweighted treatment rate).
[b] Not included subjects without oocyte retrieval (Ganirelix: 5323, 5404, 5408, 5601, 5708, 5709, 5711, 5720, 5946, 6009, 6141, 6219, 6221, 6422, 6499, 6618, 6620, 6716, 6718, 6726, 6860, 6904, 7003; Buserelin: 5128, 5224, 5302, 5704,5714, 5715, 5923, 5951, 6402, 6423, 6611, 6613, 6629, 6834, 6909, 7004, 7017)
[c] Not included subjects without embryo transfer (ganirelix: 5107, 5113, 5207, 5323, 5404, 5408, 5601, 5604, 5622, 5707, 5708, 5709, 5711, 5720, 5737, 5828, 5833, 5836, 5844, 5855, 5930, 5946, 6001, 6005, 6006, 6009, 6121, 6140, 6141, 6143, 6209, 6217, 6219, 6221, 6228, 6315, 6318, 6422, 6498, 6499, 6527, 6529, 6606, 6618, 6620, 6716, 6718, 6720, 6722, 6724, 6726, 6809, 6811, 6822, 6824, 6854, 6860, 6904, 7003, 7005, 7013, 7014, 7021, 7022; buserelin: 5128, 5224, 5302, 5419, 5704, 5712, 5714, 5715, 5730, 5847, 5923, 5951, 6004, 6202, 6214, 6308, 6320, 6329, 6402, 6423, 6510, 6611, 6613, 6629, 6834, 6902, 6909, 7004, 7017, 7028).
[e] Not included subject 5323 (ganirelix) who had an ongoing pregnancy after intrauterine insemination (IUI) (no ET), and subject 5224 (buserelin) who had a spontaneous pregnancy before recFSH treatment.
N/A = not applicable

The estimated treatment difference (ganirelix minus buserelin) was –1 oocyte and the lower bound of the one-sided 97.5% confidence limit (–1.8) was within the equivalence margin of –3 oocytes. The ongoing pregnancy rate per attempt was 20.3% for ganirelix and 25.7% for the reference treatment. The lower bound on the one-sided 97.5% confidence limit (–11.9%) is less than –5%. Therefore, the equivalence criterion for the pregnancy rate was not met. However, the Sponsor states that the study aim was not to show that the confidence interval excluded the 5% limit.

The per attempt pregnancy rate of 20.3 % for ganirelix compares favorably with the rate of 23.7 % per initiated cycle, the most recently published (1995) IVF results utilizing GnRH agonists.

Secondary efficacy parameters analyzed for efficacy include study medication treatment failure (no hCG or hCG given early because of premature luteinization) and the number of good quality embryos. These secondary efficacy parameter results are summarized as follows:

Study medication failure

In the ganirelix group, 3.5% of ITT subjects had a study medication treatment failure compared to 5.9% of ITT subjects in the buserelin group. In the ganirelix group the most reported medication treatment failures were due to insufficient ovarian response in 1.9% of ITT subjects compared to 1.7 % of ITT subjects in the buserelin group. In the buserelin treatment group the most reported treatment failure were due to insufficient down regulation in 2.9% of ITT subjects. Premature luteinization occurred in 0.4% of the ITT ganirelix subjects and no subjects on buserelin.

Number of good quality embryos

The ganirelix ITT group had 3.3 (±3.0) good quality embryos compared to 3.5 (±3.2) in the buserelin ITT group.

Also evaluated were the number of subjects with LH rise ≥10 IU/L, serum LH, recFSH dose and duration of GnRH analog and recFSH treatment. The following summarizes these results:

Serum LH rises

A total of 36 subjects (7.8%) in the ganirelix ITT group had a LH rise (LH≥ 10 IU/L). Three subjects had a LH rise ≥ 10 on day 1 of treatment (day 1 recFSH). All three of these subjects went on to embryo transfer resulting in one ongoing pregnancy. Twenty subjects (4.3 %) had a LH rise ≥10 on the day of the first ganirelix administration. Most samples (18/20) were obtained before the first ganirelix injection. Fifteen of these 20 subjects had LH levels which decreased below 10 IU/L after two days of ganirelix therapy indicating that in this small number of patients ganirelix was able to suppress LH even if levels had already risen. Nineteen of the 20 had embryo transfer resulting in 3 ongoing pregnancies, 1 ectopic pregnancy, and 1 spontaneous abortion.

Thirteen subjects (2.8 %) had a LH value ≥10 after the day of the first ganirelix injection. Seven of the thirteen were cancelled prior to embryo transfer. The other 6 subjects continued on to embryo transfer but no pregnancy resulted. A serum ganirelix level analysis of subjects with a LH rise ≥ 10 from treatment day 6 on, suggested adequate drug compliance.

In the buserelin group, three subjects had a rise in serum LH levels. One subject had the cycle cancelled. Two subjects had ET which resulted in one ongoing pregnancy.

Serum LH on the day of hCG injection

A median serum LH level of 1.63 (<0.6 – 6.92) IU/L for subjects on ganirelix therapy was similar to the median serum LH level of 1.51 (<0.6 – 4.44) IU/L for subjects on buserelin therapy.

Duration of GnRH analog treatment

The mean number of days on Ganirelix was 5.4(±2.0) days while the mean number of days on buserelin was 27.2 (± 3.8) days.

RecFSH dose and duration

The total dose of recFSH on ganirelix was 1500 IU vs 1800 IU on buserelin. The mean duration of recFSH treatment was 9.6 (± 2.0) days on ganirelix and 10.6 (±2.0) days on buserelin.

The safety profile of ganirelix was acceptable and was not substantially different from buserelin. Ovarian hyperstimulation syndrome occurred in 2.4% of the AST group on ganirelix compared to 5.9%of the AST group on buserelin. The most common AE on ganirelix was gynecologic abdominal pain, occurring in 6.9% of AST subjects. Gynecologic abdominal pain occurred in 3.4% of the buserelin AST group. The most common AE on buserelin was headache occurring in 9.7 % of the AST group and in 4.5% of the AST group on ganirelix.

Generally, the data support that the combination of efficacy and safety for ganirelix is not clinically inferior to buserelin.

Sponsor-Submitted Historical Support

The Sponsor submitted 12 publications from 1990 through 1995 that report the clinical pregnancy rate per attempt for IVF cycles with gonadotropin only stimulation. The overall mean clinical pregnancy rate, based on 1292 women was 16.5% with a range of 0-25%. Five reports from 1994 through 1997 of controlled ovarian hyperstimulation protocols utilizing GnRH agonist were summarized with an overall mean clinical pregnancy rate based on 853 women of 31.1% with a range of 19-45%. The clinical pregnancy rate per attempt of 23.3% found in study 38607 is 41% higher than that reported in the summarized literature for gonadotropin stimulation only.

20.3% JA 7/21/99

Nomenclature

The trade name Antagon as proposed by the Sponsor was accepted by the Agency..

Conclusions:

The historical data supplied from the SART IVF Registry clearly support that in controlled ovarian stimulation protocols for IVF, the use of GnRH agonists has improved the cancellation rates (failure to reach oocyte retrieval) from 25% to 30 % down to 12.5% to14 %. The historical data collected by the Sponsor's literature review and presented in the submission suggest that with the use of GnRH agonists, pregnancy rates have been 88 % higher than when agonists were not used. The published SART IVF Registry data would suggest a more modest increase in pregnancy rates ranging from 10% to 60% with the use of GnRH agonists. The assumed mechanism for GnRH is one of continuous down regulation during gonadotropin stimulation, which avoids premature endogenous LH surges.

The data from study 38607 support that the efficacy and the safety of ganirelix are not clinically inferior to the reference GnRH agonist, buserelin. This submission clearly demonstrates a mechanism for the action of the GnRH antagonist, ganirelix, in reducing the incidence of the endogenous LH surge (defined as LH≥ 10) and subsequent luteinization (progesterone ≥ 2 ng/ml). A LH surge occurred in less than 1% of subjects. The selection of the dose, which was on the basis of the proportion of subjects with LH rise (≥ 10) along with the number of cumulus-oocyte complexes and ongoing pregnancies, was appropriate. The 4.3% cancellation rate on ganirelix compares extremely favorable to SART Registry reported IVF cancellation rates with GnRH agonists. The data suggest (even though the numbers are small) that use of ganirelix can rescue cycles where the LH rise has begun before antagonist is administered. The 0.25 mg open-label pivotal trial ITT pregnancy rate of 23.3 % per ET, compares favorably to SART IVF Registry data on pregnancy rates of 21% to 31% per ET with GnRH agonists.

The safety profile of ganirelix raises no concern. The major advantage of ganirelix antagonist treatment over GnRH agonist therapy appears to be in patient convenience with fewer overall days of treatment. In study 38602 the total dose of FSH per treatment cycles was 300 IU less with ganirelix than with buserelin. This could potentially represent a cost advantage for the patient.

The data submitted in studies 38602, 38607 and 38603 representing a total of 794 subjects on ganirelix acetate (532 at the selected 0.25 mg dose) support the safety and efficacy of ganirelix acetate for the avoidance of premature LH surge. I concur with the medical officer's assessment that this NDA should be approved.

DIV

JUN 15 1999

MEDICAL OFFICER'S NDA REVIEW

NDA Number: 21-057

Applicant: Organon, Inc.
375 Mount Pleasant Avenue
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Date of Submission: January 28, 1999

Date Received: January 29, 1999

Date Review Completed: May 29, 1999

Date Review Revised: June 14, 1999

Date Review Finalized: June 14, 1999

I. General Information:

A. Name of Drug:
1. Established Name: Ganirelix acetate
2. Trade Name: Antagon
3. Laboratory Code Name: Org 37462

B. Pharmacologic Category:
Gonadotropin - releasing hormone antagonist

C. Proposed Indication: Prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation.

D. Dosage Form and Route of Administration: Sterile, isotonic, aqueous solution filled into 1 mL, ready-for-use syringes with an extractable volume of 0.5 mL for subcutaneous administration.

E. Strength: Each 1 mL glass syringe contains 250 μg /0.5 mL of ganirelix acetate.

F. Dosage: After initiating FSH therapy on Day 2 or 3 of the cycle, ganirelix acetate injection 250μg is administered subcutaneously once daily during the early to mid follicular phase and continued daily until the day of hCG administration.

G. Related Drugs: None marketed in the United States. Since 1971, more than 2,000 GnRH analogues have been synthesized. Unfortunately, first and second generation antagonistic analogues of GnRH were shown to release histamine that caused unwanted changes ranging from local wheal and flare reaction at the site of injection to generalized cardiovascular and pulmonary symptoms.

II. Manufacturing Controls:

Please refer to chemist's review for details.

III. Pharmacology:

Please refer to pharmacologist's review for details.

IV. Clinical Background:

The first successful in vitro fertilization and embryo transfer was performed after egg recovery during a spontaneous cycle. It was subsequently demonstrated that stimulation of multiple follicular development with clomiphene citrate and hMG, or hMG alone, significantly improved IVF-ET success by allowing the simultaneous transfer of more than one embryo. However, a significant proportion of these controlled hyperstimulation treatments were canceled before oocyte pickup because of premature surge of luteinizing hormone. Because of this problem and proper timing of the cycle, pre-and co-treatment of the controlled ovarian hyperstimulation cycle with a gonadotropin-releasing hormone agonist has been used successfully to control the endogenous secretion of LH by sensitization and down regulation of the pituitary gonadotropins. This co-treatment with a marketed Gn-RH agonist is now the standard treatment regimen in greater than 95% of assisted reproductive cycles in the United States, even though the use is "off label" for this indication. The use of GnRH agonist for controlled ovarian hyperstimulation has specific disadvantages such as the initial stimulation of gonadotropin release (flare-up), the long period to achieve effective pituitary suppression, and the higher dose of FSH required for controlled ovarian hyperstimulation due to suppression of endogenous FSH. In contrast, GnRH antagonists suppress gonadotropins immediately by blocking the GnRH receptor. Therefore, GnRH antagonists are more efficient than Gn-RH agonists in treatment regimen that require immediate suppression of the pituitary-gonadal axis.

V. Regulatory Background:

A. A clinical development meeting with the applicant occurred October 28, 1996.

B. A pre-NDA guidance meeting by telephone with the applicant occurred

September 9, 1998. The applicant agreed to submit historical information on spontaneous abortions, clinical pregnancies, multiple pregnancies, live births, and ovarian hyperstimulation syndrome occurring in infertile patients who were treated without the administration of a Gn-RH agonist or antagonist. FDA agreed to accept studies 38602 (phase 2 dose-finding study) and 38607 (a phase 3 efficacy and safety study) as the pivotal studies in the NDA submission.

VI. Foreign Marketing History:

Ganirelix acetate is not marketed or registered in any foreign country. The NDA registration file was to be submitted at approximately the same time to the United States, Canada, the European Union, Australia, Norway, Iceland, and Switzerland.

VII. Consultations: Please refer to Statistician's Review.

VIII. Clinical Studies:

The efficacy and safety of ganirelix acetate was evaluated in two completed, controlled, multicenter, randomized trials and one follow-up study. Studies 38602 and 38607 are the pivotal studies. In these studies, a total of 794 subjects received ganirelix acetate and 237 subjects received buserelin, a GnRH agonist not marketed in the United States. Of the 794 subjects receiving ganirelix acetate, 532 received the recommended to-be-marketed selected does of 250 μg, 165 received a higher dose, and 97 received a lower dose. Study 38603 examined parameters related to pregnancy, delivery, and neonatal outcome for subjects who became pregnant following treatment in study 38602. These three studies were located throughout Europe with one study center located in Israel and not conducted under an IND.

A. Study 38602. A Phase II, Multi-center, Double-blind, Randomized, Dose-finding Study to Assess the Efficacy of the Gn-RH antagonist Org 37462 to Prevent Premature LH Surges in Women Undergoing Controlled Ovarian Hyperstimulation With Recombinant FSH.

1. Investigators and Country:
   - P. Devroey, Belgium
   - J. Kahn, Denmark
   - L. Westergaard, Denmark
   - F. Olivennes, France
   - B. Hedon, France
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S. Paulou, Greece
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T. Abyholm, Norway
T. Hillensjo, Sweden
A. Rutherford, United Kingdom

2. Objectives of the Study:

The primary objective was to select the minimal effective dose of Org 37462 preventing premature surges of endogenous LH in women undergoing controlled ovarian hyperstimulation with recombinant FSH.

The secondary objective of the study was to prove that Org 37462 was safe and well-tolerated with respect to local reactions at the site of injection. In addition, direct effects or carry-over effects of Org 37462 on reproductive functions (steroidogenesis, oocyte maturation, corpus luteum functioning and embryo implantation) was investigated.

3. Rationale for the Study:

In current clinical practice, patients undergoing controlled ovarian hyperstimulation are treated with Gn-RH agonists ("off label" use) to prevent premature LH surges. Gn-RH agonist use results in an initial stimulation of gonadotropin release. A relatively longer treatment period with a Gn-RH agonist is required to achieve effective pituitary suppression. Thereafter, due to the suppression of endogenous FSH, a relatively high dose of FSH/hMG is required for ovarian stimulation. A Gn-RH antagonist, like Org 37462, suppresses gonadotropins directly from the start of administration. This implies a relatively short treatment with Org 37462 for only a few days during FSH stimulation, i.e. when there is an increased risk of rises of endogenous LH.

4. Method of Assignment to Treatment:

Eligible subjects fulfilling all of the inclusion criteria and none of the exclusion criteria obtained their subject number from a randomization list and were assigned to one of the six treatment groups.

5. Number of Subjects:

A total of 360 subjects were to be recruited in order to guarantee 300 evaluable subjects (50 evaluable subjects/dosage group).

6. Duration of Clinical Trial:

One treatment cycle only.

7. Inclusion Criteria:

- Females of infertile couples for whom the cause of infertility is potentially solvable by COH and IVF with or without ICSI
- 18 to 39 years of age at the time of screening
- Body weight between 50 and 75 kg with a BMI of 18-29
- Normal menstrual cycle of 24-35± 3 days
- Willing to give written informed consent

8. Exclusion Criteria:

- History of/or current endocrine abnormality such as polycystic ovary syndrome, hyperprolactinemia, or evidence of ovarian dysfunction
- History of non-or low-ovarian response to FSH/hMG treatment
- Abnormal cervical (Pap) smear
- History of /or current Type I hypersensitivity
- Any hormone value outside the reference range during the early follicular phase
- Any clinically significant abnormal laboratory value
- Any ovarian and/or abdominal abnormality that would interfere with adequate ultrasound investigation
- Any contraindication to the use of gonadotropins

- Use of hormonal preparations within 1 month of screening

- Systolic B.P.>150 mm Hg and/or diastolic B.P.>90mm Hg or treated hypertension

- Epilepsy, diabetes, cardiovascular, gastrointestinal, hepatic, renal, pulmonary, or abdominal disease

- Administration of investigational drugs within 3 months of screening

9. Trial Period:

June, 1996 - May, 1997

10. Dosage and Mode of Administration:

Recombinant FSH treatment was started on day 2 of the menstrual cycle with a fixed dose of 150 IU administered for 5 days, subcutaneously. The dose was then adjusted depending on the individual ovarian response as assessed by daily ultrasound. Treatment was continued until at least 3 follicles ≥ 17mm were observed.

Ganirelix acetate was administered daily subcutaneously in the abdominal wall around the umbilicus beginning after 5 days of recombinant FSH treatment and continued until and including the last day of recombinant FSH administration at a dose of either 2 mg, 1mg, 0.5 mg, 0.25 mg, 0.125 mg, or 0.0625 mg.

Human chorionic gonadotropin, 10,000 IU was administered either subcutaneously or intramuscularly as soon as at least 3 follicles ≥ 17mm were observed by ultrasound.

Progesterone 300 mg intravaginally or 25 mg intramuscularly was usually administered for 2 weeks for luteal phase support beginning at the latest on the day of embryo transfer.

11. Efficacy Assessments:

The primary efficacy variable was the occurrence of an LH rise≥ 10 IU/L during treatment as analyzed at the central laboratory.

Other parameters analyzed included the number of cumulus-oocyte complexes, the ongoing pregnancy rate, study medication treatment failure, number of good quality embryos, the number of ganirelix acetate and recombinant FSH treatment days, the total dose of recombinant FSH used, hormone concentrations, numbers of follicles on the day of hCG, number of zygotes, fertilization rate, implantation rate, spontaneous abortions, ectopic pregnancies, multiple pregnancies, clinical pregnancies, and the take-home baby rate.

12. Safety Assessments:

Adverse events, vital signs, laboratory parameters, intradermal tolerance assessment, and local tolerance at the injection site were evaluated.

13. Disposition of Subjects:

A total of 342 women were randomized, of whom 332 received treatment with ganirelix acetate. Of this population, 292 subjects had embryo transfer as indicated in Table 1. Of 70 subjects who received at least one injection of 0.25 mg ganirelix acetate, only three did not receive an hCG injection.

Table1
(Sponsor's Table 2)
Disposition of Subjects by Treatment Stage

Treatment Stage	Total	Treatment Group (mg)					
		0.0625	0.125	0.25	0.5	1	2
Randomized	342	31	70	73	69	68	31
FSH	333	31	66	71	69	66	30
Ganirelix	332	31	66	70	69	66	30
hCG	321	29	66	67	64	65	30
OPU	319	28	66	67	63	65	30
Incubation	317	28	66	66	62	65	30
ET	292	27	61	62	54	61	27

14. Major Protocol Violations:

Three subjects were excluded from the Per Protocol subject data set because of major protocol violations.

15. Demographic Characteristics:

Treatment groups were similar with respect to age, body height, weight, body mass index, duration of infertility, cause of infertility, and type of infertility as indicated in Table 2.

Table 2
(Sponsor's Tables 9, 10, and 11)
Demographics
Treatment Group (mg)

	0.0625	0.125	0.25	0.5	1	2
Mean age (years)	31.6	31.9	31.4	31.5	31.7	31.9
Mean Ht (cm)	163.6	166.5	164.7	164.8	166.5	165.1
Mean Wt (kg)	61.0	62.8	61.5	61.5	63.4	61.6
Mean BMI (Kg/m^2)	22.8	22.7	22.7	22.6	22.9	22.6
Infertility (yrs)	5.2	5.3	5.2	5.1	5.0	5.1
1° Infertility (%)	58.1	60.0	58.0	58.0	58.5	56.7

16. Results:

a. Efficacy:

1.) LH Rises During Ganirelix Treatment:

The incidence of LH rises decreased with increasing doses of ganirelix acetate when three subjects whose ganirelix levels indicated noncompliance were excluded as indicated in Table 3.

Table 3
(Sponsor's Table 18)
Number and Percentage of Subjects with LH Rises during Ganirelix acetate Treatment (Per-Protocol Group)

Treatment Group (mg)

	0.0625 N=31	0.125 N=65	0.25 N=69	0.5 N=69	1 N=65	2 N=30	Total N=329
LH Rises (%)	5 (16.1)	6 (9.2)	1 (1.4)	0	0	0	12 (3.6)

2.) Serum LH on the Day of the hCG Injection (Per-Protocol Group):

Serum LH levels decreased with increasing doses of ganirelix acetate. As indicated in Table 4, on the day of hCG administration, median values of serum LH ranged from 3.56 IU/L in the 0.0625 mg dose group to 0.35 IU/L in the 2mg dose group.

Table 4
(Sponsor's Table 20)
Median Serum LH . on the Day of the hCG Injection
Restricted to Subjects with an hCG Injection (Per-Protocol Group)

	Treatment Group (mg)					
	0.0625 N=28	0.125 N=62	0.25 N=65	0.5 N=62	1 N=61	2 N=26
Serum LH (IU/L)	3.56	2.46	1.73	1.02	0.57	0.35
Range	0.55-19.9	0.59-11.4	<0.25-6.41	0.39-4.72	<0.25-2.18	<0.25-0.83

3.) Median Serum Estradiol on the Day of the hCG Injection:

Table 5 shows the median serum concentration of estradiol during ganirelix acetate treatment. Rises in serum estradiol were observed during ovarian stimulation in all treatment regimens, but the use of increasing doses of ganirelix acetate led to smaller estradiol increases.

Table 5
(Sponsor's Table 21)
Median Serum Estradiol Values on the Day of the hCG Injection
Restricted to Subjects with an hCG Injection (Per-Protocol Group)

	Treatment Group (mg)					
	0.0625 N=28	0.125 N=62	0.25 N=65	0.5 N=62	1 N=61	2 N =26
Serum E_2 (pg/mL)	1475	1130	1160	823	703	430
E_2 Range	645-3720	462-3780	384-3910	279-2720	284-2340	166-884

4.) Follicles≥ 11mm on the Day of the hCG Injection, per attempt, Per-Protocol Group:

Little difference between the treatment groups was found with respect to the number of follicles ≥11mm on the day of hCG injection. The same was true for the number of follicles ≥ 15 mm and ≥ 17 mm. In each instance, the 0.25 mg group had the highest mean outcome, however.

Table 6
(Sponsor's Table 22)
Number of Follicles ≥ 11 mm on the Day of hCG Injection, per Attempt, Per-Protocol Group

	0.0625 N=30	0.125 N=65	0.25 N=69	0.5 N=69	1 N=64	2 N=26
Mean (SD)	10.3 (5.40)	10.7 (4.78)	11.4 (4.95)	9.4 (5.24)	10.5 (4.56)	9.4 (3.56)

5.) Cumulus - Oocyte - Complexes:

As can be seen in Table 7, there was little difference between the treatment groups with respect to the number of cumulus -oocyte-complexes. The 0.25 mg dose group, however, had the highest mean values.

Table 7
(Sponsor's Table 25)
Total Number of Cumulus-Oocyte - Complexes, per Attempt, per-Protocol Group

Treatment Group (mg)

	0.0625 N=30	0.125 N=64	0.25 N=69	0.5 N=69	1 N=64	2 N=26
Mean (SD)	9.0 (5.66)	9.6 (5.41)	10.0(5.39)	8.8(6.55)	9.3 (6.00)	8.6 (4.41)

6.) Embryos Obtained:

The total number of embryos obtained is presented in Table 8.

Table 8
Sponsor's Table 28
Total Number of Embryos Obtained per Attempt, Per-Protocol Group

	Treatment Group (mg)					
	0.0625 N=30	0.125 N=65	0.25 N=68	0.5 N=69	1 N=64	2 N=26
Mean (SD)	5.4 (3.57)	5.9 (4.32)	5.4 (4.43)	4.6 (4.19)	5.3 (3.89)	4.9 (3.67)

7.) Embryos Transferred:

The total number of embryos transferred is presented in Table 9.

Table 9
(Sponsor's Table 39)

Total Number of Embryos Transferred, Restricted to Subjects with Embryo Transfer, Per-Protocol Group

	Treatment Group (mg)					
	0.0625 N=27	0.125 N=60	0.25 N=62	0.5 N=54	1 N=59	2 N=23
Mean (SD)	2.7 (0.92)	2.6 (0.96)	2.4 (0.86)	2.3 (0.63)	2.4 (0.77)	2.7(1.06)

The total number of good quality embryos was essentially the same for all dose groups.

8.) Implantation Rate:

The implantation rate is the ratio of the number of gestational sacs and the number of embryos transferred. As can be seen in Table 10, treatment with 0.25 mg of ganirelix acetate resulted in the highest implantation rate. In the three highest treatment groups, the lowest mean implantation rates were observed, although similar numbers of embryos were transferred in all treatment groups as seen in table 9.

Table 10
(Sponsor's Table 29)
Implantation Rate Restricted to Subjects with Embryo Transfer
Per-Protocol Group

	Treatment Group (mg)					
	0.0625 N=27	0.125 N=60	0.25 N=62	0.5 N=54	1 N=59	2 N=23
Mean (SD)	14.2 (27)	16.6 (31)	21.9 (31)	9.0 (24)	8.8 (22)	1.5 (7)

9.) Intrauterine Vital Pregnancy per Attempt:

An intrauterine vital pregnancy is defined as "proof of at least one fetus with heart activity as assessed by ultrasound 5 to 6 weeks after embryo transfer." The number of vital intrauterine pregnancies and the rate per attempt are presented in Table 11.

Table 11
(Sponsor's Table 30)
Number of Intrauterine Vital Pregnancies and the Rate per Attempt
per-Protocol Group

	Treatment Group (mg)					
	0.0625 N=30	0.125 N=65	0.25 N=68	0.5 N=69	1 N=64	2 N=26
n (%)	7 (23.3)	17 (26.2)	25 (36.8)	8 (11.6)	9 (14.1)	1 (3.8)

10.) Intrauterine Vital Pregnancy per Transfer:

The number of vital intrauterine pregnancies and the rate per transfer are presented in Table 12.

Table 12
(Sponsor's Table 31)
Number of Intrauterine Vital Pregnancies and the Rate per-Transfer, per-Protocol Group

Treatment Groups (mg)

	0.0625 N=27	0.125 N=60	0.25 N=62	0.5 N=54	1 N=59	2 N=23
n (%)	7 (25.9)	17 (28.3)	25 (40.3)	8 (14.8)	9 (15.3)	1 (4.3)

b. Safety:

A total of 53 subjects (16.0%) experienced at least one adverse event and the incidence of adverse events was similar between the dose groups. Eleven subjects (3.3%) had in total 18 adverse events which were reported as possibly or probably drug related. In the 0.25 mg dose group, 3 subjects reported gynecological abdominal pain, 2 subjects reported ovarian hyperstimulation syndrome, and 1 subject each reported acne, headache, abdominal pain, postural hypotension, coughing, pharyngitis, upper respiratory tract infection, positive cervical smear, miscarriage, and ectopic pregnancy.

The percentage of subjects with a moderate or severe local tolerance reaction 1 hour after any of the ganirelix acetate injections was 21.7 %. Only 4.2% of the subjects still experienced a reaction 24 hours after injection. Moderate or severe skin redness was reported most frequently 1 hour after injection (overall 19.6%). This parameter appeared to be related to the dose of ganirelix acetate, as the incidence increased from 3.2% in the 0.0625 mg group to 17.1% in the 0.25 mg group to 33.3% in the 2 mg group. Swelling also tended to occur more frequently in the higher dose groups.

After enrollment, each subject had an intradermal injection of ganirelix acetate to assess intradermal tolerance. This had no predictive value for the possible occurrence of hypersensitivity reactions.

16. Reviewer's Comments:

Study 38602 is a phase 2, multi-center, double-blind, randomized, dose-finding study to select the minimal effective dose of ganirelix acetate during one cycle of treatment in women undergoing controlled ovarian hyperstimulation with recombinant FSH. Selection of the optimal dose was based on the efficacy of ganirelix acetate in preventing LH surges, number of follicles, number of oocytes, number of good quality embryos, and the vital pregnancy rate. The 0.125 mg and 0.25 mg doses were the only ones selected based on these outcomes. However, the 0.125 mg dose did not sufficiently prevent LH rises (LH ≥ 10 IU/L) during ovarian stimulation and , therefore, the 0.25 mg dose was selected as the optimal minimal effective dose. This selection is valid and appropriate.

Six dosage groups had been planned with 50 subjects randomized to each group, but the lowest and highest dosage groups were stopped before completion of the study so these two treatment arms contained fewer subjects. This decision was based on the advice of an External Independent Advisory Committee which had been formed to advise the sponsor on stopping a treatment arm in case of LH rises during ganirelix acetate treatments. Since the start of the study, some investigators had informed the sponsor about cases of extremely low serum LH and falling estradiol concentrations as well as follicle growth arrest after starting ganirelix acetate treatment. The committee reviewed these cases.

In addition, the committee reviewed all rises of LH≥ 15 IU/L according to the local laboratory and ≥10 IU/L according to the central laboratory that occurred during ganirelix acetate treatment. Based on the committee's review and evaluation, randomization to the highest and lowest dose arms was stopped. Investigators were informed as to which subject numbers were not to be assigned. The curtailment of these two treatment arms did not interfere with the selection of the minimal effective dose and was carried out in accordance with section 15.4 of the protocol (Decision Criteria to Discontinue a Dosage Group) which states in part, "When unblinding of codes of these subjects (high LH) indicates that one or more Org 37462 dosages are ineffective, these treatment groups will be discontinued during the study".

The inclusion and exclusion criteria are acceptable.

The primary efficacy parameter (serum immunoreactive LH during Org 37462 treatment as measured by the central laboratory) is appropriate to select the minimal effective dose of ganirelix acetate that prevents premature LH surges of endogenous LH in women undergoing controlled ovarian hyperstimulation with recombinant FSH. The selection of the minimal effective dose primarily was based on the per-protocol analysis since the group of subjects in this analysis generally maximizes the opportunity for a new treatment to show efficacy and most closely reflects the scientific model underlying the protocol.

No subjects discontinued the study because of an adverse event. The most serious adverse event occurring was moderate ovarian hyperstimulation syndrome which occurred in two subjects. This is known to occur with the administration of FSH and unlikely to be directly attributable to the administration of ganirelix acetate.

Pregnancies occurring in the study were followed up and reported under protocol 38603.

Local reactions at the site of injection of ganirelix acetate did occur. This was usually redness at one hour after injection (19.6% of subjects had moderate or severe redness) which by 24 hours after injection was present only moderately and in only 1.2% of subjects.

The 4.3% cancellation rate in the 0.25 mg dose group is an exceptionally low and desirable rate.

Overall ganirelix acetate is safe, well-tolerated, and a daily dose of 0.25 mg which prevented LH rises in women undergoing controlled ovarian hyperstimulation is the optimal minimal effective dose.

B. Study 38607. A Phase III. Multi-Center. Open-label. Randomized Study to Assess the Efficacy and Safety of Org 37462 Treatment in Women Undergoing Controlled Ovarian Hyperstimulation. Using a Long Protocol of Buserelin as a Reference Treatment.

1. Investigators and Country:

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A. Pellicer	Spain
J. Hughes	France
F. Olivennes	France
D. Barlow	United Kingdom
A. Rutherford	United Kingdom
B. Tariatzis	Greece
S. Pavlou	Greece
T. Abyholm	Norway
V. Von During	Norway
F. Fauser	The Netherlands
C. Jansen	The Netherlands
L. Hamberger	Sweden
T. Hillensjo	Sweden

2. Objective of the Study:

The objective was to assess that Org 37462 treatment is efficacious, safe, and well-tolerated in women undergoing controlled ovarian hyperstimulation.

3. Rationale for the Study:

Gonadotropin releasing hormone agonists are used nowadays in almost all assisted reproduction techniques centers to avoid premature luteinizing hormone rises and to enable efficient organization of large, controlled ovarian hyperstimulation programs. However, specific disadvantages of GnRH agonists are the initial flareup, the rather long period until pituitary suppression becomes effective, and, possibly the higher dose of FSH required due to suppression of endogenous FSH. The use of GnRH agonists for this purpose is "off label" in the United States. No sponsor has obtained approval of a drug for this indication. In contrast, GnRH antagonists suppress gonadotropins immediately by blocking the GnRH receptor. Therefore, GnRH antagonists have potential advantages over GnRH agonists in any treatment requiring immediate suppression of the pituitary-gonadal axis.

A multi-center, double-blind, dose-finding study with ganirelix acetate was conducted to select the minimal effective dose. Based on the incidence of LH rises (≥10 IU/L), the clinical outcome, safety, and local tolerance to ganirelix acetate, a daily subcutaneous dose of 0.25mg was selected. Study 38607 was designed to demonstrate that the selected therapeutic dose of 0.25 mg is efficacious and safe in female partners of infertile couples undergoing controlled ovarian hyperstimulation with or without intra cytoplasmic sperm injection. It included a group of women undergoing controlled ovarian hyperstimulation with a conventional, long-term protocol using buserelin as a reference.

4. Method of Assignment to Treatment:

Only subjects who fulfilled all inclusion criteria and violated none of the exclusion criteria were randomized into the study and assigned to the ganirelix or the buserelin group. To improve balance, the randomization was stratified for IVF with or without ICSI and for primary or secondary infertility.

5. Number of Subjects:

A total of 660 women were to be recruited in order to guarantee 600 evaluable subjects with approximately 400 subjects assigned to ganirelix and 200 subjects to buserelin.

6. Duration of Clinical Trial:

One treatment cycle only.

7. Inclusion Criteria:

- Female partners of infertile couples for whom COH and IVF with or without ICSI is indicated.
- 18-39 years of age at the time of screening.
- Body mass index ≥18 and ≤29Kg/m^2.
- Normal menstrual cycle with a range of 24-35± 3 days.
- Willing to give written informed consent.

8. Exclusion Criteria:

- History of/or current endocrine abnormality such as polycystic ovary syndrome, hyperprolactinemia or evidence of ovarian dysfunction.
- History of non-or low-ovarian response to FSH/hMG treatment.
- Abnormal cervical (Pap) smear.
- Current Type I hypersensitivity.
- Any hormone value outside the reference range during the early follicular phase.
- Any clinically significant abnormal laboratory value.
- Any ovarian and/or abdominal abnormality that

would interfere with adequate ultrasound investigation.

- Any contraindication to the use of gonadotropins.

- Use of hormonal preparations within 1 month of screening.

- Systolic B.P. >150 mm Hg and/or diastolic B.P.> 90 mm Hg or currently treated hypertension.

- Epilepsy, diabetes, cardiovascular, gastrointestinal, hepatic, renal, pulmonary, or abdominal disease.

- Administration of investigational drug within 3 months of screening.

- Known sensitivity to GnRH or its analogs

- Pregnancy or lactation.

- Undiagnosed vaginal bleeding.

- Hypersensitivity to any of the substances in recombinant FSH.

- Ovarian cysts in both ovaries or both ovaries enlarged (not related to PCOS).

- Malformation of the sexual organs incompatible with pregnancy.

- Fibroid tumors of the uterus incompatible with pregnancy.

- Alcohol or drug abuse, or history thereof, within 12 months preceding signing informed consent.

- Any subject previously randomized in the dose-finding study (protocol 38602).

9. Trial Period:

September 1997-August 1998

10. Dosage and Mode of Administration:

Table 13 shows a summary of the dosing schedule for all hormone treatments.

Table 13
(Sponsor's Table 1)
Dosing Schedule for Hormone Treatments

Ganirelix	- start rec FSH on day 2 or 3 of cycle
	- start ganirelix on day 6 of rec FSH treatment
	- up to 14 days of ganirelix +19 days of rec FSH
Buserelin	- start buserelin on day 21-24 of cycle
	- start recFSH after 14-28 days of buserelin
	- up to 19 days of rec FSH + 19 days of buserelin
hCG	- when at least 3 follicles ≥ 17mm
Progesterone	- start at the latest on day of ET
	- for 2 weeks or up to menses
	- several additional weeks, in case of pregnancy

Recombinant FSH treatment of the ganirelix group started at day 2 or 3 of the menstrual cycle, administered once daily by subcutaneous injection in the abdominal wall. From day 1 through day 5 of recombinant FSH treatment, the daily dose of recombinant FSH was fixed at 150 I.U. From treatment day 6 onwards, the daily dose of recombinant FSH was adjusted depending on individual ovarian responses up to, but not including the day of hCG injection. The maximal duration of recombinant FSH treatment was 19 days.

Ganirelix treatment started on day 6 of recombinant FSH treatment for a maximal duration of 14 days.

Pretreatment with buserelin started between day 21 and 24 of the menstrual cycle (mid luteal phase) with daily doses of 0.6 mg intranasally. Buserelin puffs (0.15 mg each) were taken four times a day for a maximum of 28 days. After down-regulation, buserelin was continued for up to 19 additional days.

Recombinant FSH treatment started after 14 days of buserelin intake if a hypogonadotropic state was reached (serum E_2 <50pg/ml or <200pmol/l). If down regulation was not achieved, recombinant FSH treatment was postponed and the daily dose of buserelin was doubled to 1.2 mg and continued for a maximum of 4 weeks. The dose of buserelin by which down-regulation was established was used during the remainder of the buserelin treatment.

Human chorionic gondadotropin, 10,000 I.U. was administered either subcutaneously or intramuscularly at any suitable injection site when at least 3 follicles ≥17mm. In cases of risk for OHSS, the dose of hCG was reduced to 5,000 I.U.

Progesterone (300 mg intravaginally or 25 mg intramuscularly) was given daily for 2 weeks or up to menses starting at the latest on the day of embryo transfer. Luteal phase support could be continued for several additional weeks.

11. Efficacy Assessments:

Primary efficacy parameters were the number of oocytes retrieved and the ongoing pregnancy rate. The study treatment failure and the number of good quality embryos obtained (grade 1 or 2) were secondary efficacy parameters.

12. Safety Assessments:

Adverse events, vital signs, laboratory parameters, and local tolerance at the injection site were evaluated.

13. Disposition of Subjects:

A total of 730 subjects were randomized, 486 to the ganirelix group and 244 to the buserelin group (2:1 ratio). Of this population, 399 ganirelix subjects and 208 buserelin subjects had embryo transfers as indicated in Table 14.

Table 14
(Sponsor's Table 5)
Number (%) of Subjects by Treatment Group and Treatment Stage
All Subjects Randomized

	Treatment Group		
Treatment Stage	Ganirelix	Buserelin	Total
Randomized	486 (100%)	244 (100%)	730 (100%)
Buserelin	NA	237 (97.1%)	237 (32.5%)
FSH	463 (95.3%)	228 (93.4%)	691 (94.7%)
Ganirelix	460 (94.7%)	2 (0.8%)*	462 (63.3%)
hCG	448 (92.2%)	224 (91.8%)	672 (92.1%)
OPU	440 (90.5%)	221 (90.6%)	661 (90.5%)
Incubation	437 (89.9%)	221 (90.6%)	658 (90.1%)
ET	399 (82.1%)	208 (85.2%)	607 (83.2%)

* Two subjects were randomized to buserelin, but treated with ganirelix.

14. Major Protocol Violations:

Thirty subjects were excluded from the per-protocol subject data set because of major protocol violations, 19 (4.1%) from the ganirelix group and 11 (4.6%) from the buserelin group. Most of these (26 subjects) were subjects who had LH or FSH values equal to or above 10 IU/L at screening.

15. Demographic Characteristics:

Treatment groups were similar with respect to age, body height, weight, and body mass index. The overall mean age, body height, weight, and body mass index were 31.9 years, 166.6 cm, 63.8 kg and 23 Kg/m^2, respectively. The vast majority of subjects participating in the study were Caucasian (98% in both treatment groups).

16. Results:

a. Efficacy:

1.) Oocytes:

The number of cumulus-oocyte-complexes per treatment group are presented per attempt (both the ITT and the PP groups) in Table 15.

Table 15
(Sponsor's Table 20)
Total Number of Cumulus-Oocyte-Complexes, per Attempt (ITT)

	Treatment Group	
	Ganirelix N=463	Buserelin N=238
Mean (SD)	8.7 (5.6)	9.7 (6.2)

Total Number of Cumulus-Oocyte-Complexes, per Attempt (PP)

	Treatment Group	
	Ganirelix N=444	Buserelin N=227
Mean (SD)	8.7 (5.6)	9.8 (6.3)

2.) Ongoing Pregnancy:

The ongoing pregnancy rates per treatment group are presented per attempt and per embryo transfer (ITT groups) in Table 16.

Table 16
(Sponsor's Table 21)
Ongoing Pregnancy Rate (ITT Group)

	Treatment Group	
	Ganirelix	Buserelin
per attempt	N=463	N=237
n (%)	94 (20.3%)	61 (25.7%)
per ET	N=399	N=207
n (%)	93 (23.3%)	60 (29.0%)

Multifetal pregnancies occurred in 23.4% of ganirelix and 29.5% of buserelin subjects. Abortion occurred in 12.0% of ganirelix subjects and 13.9% of buserelin subjects.

3.) Study Medication Treatment Failure:

A cycle was considered a study medication treatment failure if a subject did not have an hCG injection or if the hCG injection was given because of premature luteinization. Table 17 shows that 16 ganirelix subjects (3.5%) and 14 buserelin subjects (5.9%) had treatment failures. In the ganirelix group, most treatment failures were due to "insufficient ovarian response" (1.9%) which was comparable to the buserelin group (1.7%). In the buserelin group, most treatment failures were due to "insufficient down regulation" (2.9%).

Table 17
(Sponsor's Table 22)
Study Medication Treatment Failures (ITT Groups)

	Treatment Group	
	Ganirelix	Buserelin
	N=463	N=238
Reason for Failure	n (%)	n (%)
Premature luteinization	2 (0.4%)	0
Risk of OHSS	0	0
Insufficient ovarian response	9 (1.9%)	4 (1.7%)
Insufficient down regulation	NA	7 (2.9%)
Other reasons	5 (1.1%)	3 (1.3%)

4.) Good Quality Embryos:

The number of good quality embryos obtained (embryos of grade 1, excellent or grade 2, good) are presented in Table 18 for the ITT group.

Table 18
(Sponsor's Table 23)
Number of Good Quality Embryos, per Attempt , (ITT)

	Treatment Group	
	Ganerelix	Buserelin
	N=463	N=238
Mean (SD)	3.3 (3.0)	3.5 (3.2)

5.) Duration of GnRH Analog Treatment:

The duration of treatment with ganirelix and buserelin is presented in Table 19 for all subjects in the AST group who had an hCG injection.

Table 19
(Sponsor's Table 24)
Duration of GnRH Analog Treatment in Subjects Receiving hCG

(AST Group)

	Treatment Group	
	Ganirelix N=450	Buserelin N=222
Mean (SD)	5.4 (2.0)	27.2 (3.8)

6.) Duration of r-FSH Treatment in Subjects receiving hCG:

The median number of days of recombinant FSH treatment is presented in Table 20 for all subjects in the AST group who had an hCG injection.

Table 20
(Sponsor's Table 24)
Duration of r-FSH Treatment in Subjects Receiving hCG
(AST group)

	Treatment Group	
	Ganirelix N=450	Buserelin N=222
Mean (SD)	9.6 (2.0)	10.6 (2.0)

7.) Serum LH on Day of hCG:

Median serum LH levels are presented in Table 21 for all subjects who received hCG to trigger ovulation.

Table 21
(Sponsor's Table 28)
Serum LH Levels on Day of hCG Injection (ITT Groups)

	Treatment Group	
	Ganirelix N=440	Buserelin N=218
Median	1.63	1.51
P5 - P95	<0.6 - 6.92	<0.6 - 4.44

8.) Table 22 shows serum E_2 levels during r-FSH treatment for all subjects who received hCG to trigger ovulation in the ITT groups.

Table 22
(Sponsor's Table 30)
Serum E_2 Levels on Day of hCG Injection (ITT Groups)

	Treatment Group	
	Ganirelix N=441	Buserelin N-218
Median	1190	1700
P5 - P95	373-3105	527-4070

9.) Number of Follicles ≥11mm on Last USS Before hCG:

The numbers of follicles larger than 11mm or equal to 11mm on the last ultrasound assessment before hCG are presented in Table 23 for both treatment groups.

Table 23
(Sponsor's Table 36)
Number of Follicles ≥ 11mm on Last USS Before hCG

	Treatment Groups	
	Ganirelix N=445	Buserelin N=224
Mean (SD)	10.7 (5.3)	11.8 (5.4)

10.) Fertilization Rate:

Mean fertilization rates were 62.1% for both treatment groups as shown in Table 24.

Table 24
(Sponsor's Table 40)
Fertilization Rates (ITT)

	Treatment Group	
	Ganirelix N=437	Buserelin N=221
Mean (SD)	62.1% (28%)	62.1% (25%)

11.) Embryos Obtained:

The total numbers of embryos obtained after incubation of zygotes are presented in Table 25.

Table 25
(Sponsor's Table 41)
Numbers of Embryos Obtained (ITT)

	Treatment Group	
	Ganirelix N=437	Buserelin N=221
Mean (SD)	6.0 (4.5)	7.1 (5.2)

12.) Numbers of Embryos Transferred:

Table 26 shows the total numbers of embryos transferred.

Table 26
(Sponsor's Table 42)
Numbers of Embryos Transferred (ITT)

	Treatment Group	
	Ganirelix N=399	Buserelin N=208
Mean (SD)	2.2 (0.6)	2.2 (0.6)

13.) Implantation Rates:

Mean implantation rates were 15.7% and 21.8% for the ganirelix and buserelin groups, respectively as shown in Table 27.

Table 27
(Sponsor's Table 43)
Implantation Rates (ITT)

	Treatment Group	
	Ganirelix N=399	Buserelin N=208
Mean (SD)	15.7% (29%)	21.8% (34%)

b. Safety:

Adverse reactions reported in more than 1% of subjects are presented in Table 28.

Table 28
(Sponsor's Table 47)
Adverse Events Reported in More than 1% of Subjects (AST)

	Treatment Group	
	Ganirelix	Buserelin
Adverse Event	N=463	N=236
Dizziness	2 (0.4%)	3 (1.3%)
Headache	21 (4.5%)	23 (9.7%)
Abdominal Pain (G.I.)	5 (1.1%)	4 (1.7%)
Nausea	5 (1.1%)	4 (1.7%)
U.R.I.	4 (0.9%)	4 (1.7%)
Anemia	1 (0.2%)	3 (1.3%)
Abdominal Pain (Gyn)	32 (6.9%)	8 (3.4%)
Dysmenorrhea	0 (0%)	8 (3.4%)
OHSS	11 (2.4%)	14 (5.9%)
Vaginal Bleeding	12 (2.6%)	8 (3.4%)
Missed Abortion	7 (1.5%)	3 (1.3%)
Fetal Death	14 (3.0%)	13 (5.5%)
Injection Site Reaction	9 (1.9%)	5 (2.1%)

A total neutrophil count ≥ 8.3* 10^9/L was noted in 55 of 423 subjects (13.0%) treated with ganirelix and in 36 of 210 subjects (17.1%) treated with buserelin (range up to 16.8* 10^9/L). A lymphocyte count ≤ 1.0* 10^9/L was noted in 23 of 423 subjects (5.4%) treated with ganirelix and in 9 of 210 subjects (4.3%) treated with buserelin.

Also, a notable upward shift was found for the total neutrophil count in both the ganirelix (21.3% of 423 subjects) and buserelin (23.8% of 210 subjects) groups.

A notable downward shift was found for the monocyte count (10.6% of 423 ganirelix subjects and 5.2% of 210 buserelin subjects). A downward shift was found for hematocrit (6.8% of 400 ganirelix subjects and 13.2% of buserelin subjects).

A downward shift was observed also for total bilirubin (7.9% of 429 ganirelix subjects and 8.0% of 213 buserelin subjects. The percentage of subjects with at least one moderate or severe local reaction during ganirelix treatment was 16.6%, 2.0%, and 2.7% at 1,4, and 24 hours after the ganirelix injection, respectively. One hour after injection, moderate or severe skin redness (9.5%) or swelling (9.5%) were most frequently reported, but 4 hours after injection, these reactions had mostly disappeared. Twenty-four hours after injection, moderate or severe bruising was most frequently reported (2.5%).

OHSS occurred in 2.4% of ganirelix subjects and 5.9% of buserelin subjects.

17. Reviewer's Comments:

Study 38607 is the pivotal study demonstrating the efficacy and safety of ganirelix in women undergoing controlled ovarian hyperstimulation, using a long protocol of buserelin as a reference treatment. A daily subcutaneous dose of 0.25 mg of ganirelix was selected for administration in this study based on the results of study 38602, a dose-finding study of the minimal effective dose based on the incidence of LH rises ≥ 10 IU/L according to the central LH immunoassay. Study 38607 is a multi-center, open-label, randomized clinical trial conducted outside of the United States. Buserelin is a Gn-RH agonist which is not available in the United States. Each subject in the study was treated for one cycle only. The inclusion and exclusion criteria are appropriate. For labeling purposes, it should be noted that subjects excluded from study included those with a history of/or current endocrine abnormality such as polycystic ovary syndrome, a history of no or low ovarian response to FSH/hMG treatment, subjects with known hypersensitivity to GnRH or its analogs, and subjects with current type I hypersensitivity (urticaria, eczema, hay fever, asthma, house dust, etc.). Clinical outcomes were primary (number of cumulus-oocyte-complexes and ongoing pregnancy rate) and secondary (no hCG injection or hCG because of premature luteinization and number of good quality embryos) efficacy parameters. For the number of cumulus-oocyte-complexes, the difference between ganirelix and buserelin was within the equivalence margin (8.7 vs 9.7). The ongoing pregnancy rates per attempt were 20.3% in the ganirelix group and 25.7% in the buserelin group. The difference between ganirelix and buserelin was almost at the equivalence margin. The study was designed as a non-inferiority trial to show that the combination of efficacy, safety, and convenience of ganirelix treatment was not clinically inferior to current care, i.e., Gn-RH agonist treatment in a long protocol. For cumulus-oocyte-complexes, the margin was - 3 oocytes. For the ongoing pregnancy rate per attempt, a treatment difference within a margin of -5% was considered to be acceptable taking into account an expected ongoing pregnancy rate of about 22%. These margins are reasonable. A median serum LH level of 1.63 on the day of hCG in ganirelix subjects with an upper range limit of 6.92 is very impressive. This is also true for buserelin where subjects had a median serum LH level of 1.51 on the day of hCG with an upper range limit of 4.44. The incidence of 2.4% OHSS in ganirelix subjects and 5.9% OHSS in buserelin subjects suggests that ganirelix may be safer than buserelin. However, no buserelin subjects had a severe case of OHSS while two ganirelix subjects did (both became pregnant).

The main advantage of ganirelix treatment is patient convenience (and presumably cost) since the overall duration of treatment with GnRH analog was significantly shorter in ganirelix subjects (5.4 days) than in buserelin subjects (27.2 days)

As no antagonist was available to serve as comparator and no agonist is approved for this indication in the United States, buserelin was chosen as a reference in this study. Although the regimens for ganirelix and buserelin are fundamentally different and the study could not be blinded, the protocol was designed so that the study did not bias in favor of either treatment arm.

In general, adverse events were the same for both regimens, except that OHSS occurred less in ganirelix subjects.

Ganirelix appears to be safe, effective, and convenient for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation. It is impossible, however, to totally isolate the efficacy of ganirelix from the efficacy of the entire treatment regimen. Of 460 subjects receiving ganirelix, 448 (97.4%) received hCG and 440 (95.7%) had oocyte retrieval. Of 237 subjects receiving buserelin, 224 (94.5% received hCG and 221 (93.2%) had oocyte retrieval.

C. Study 38603. Pregnancy and Delivery Follow-up of Protocol 38602

No study drug was administered in this study. It was a follow-up of pregnancies that occurred in subjects participating in study 38602.

A total of 68 vital intrauterine pregnancies occurred in study 38602, a dose-finding study. These pregnancies included 52 singletons, 11 twins and 5 triplets. Pregnancy outcome data was collected for 67 subjects. No follow-up data was available for subject 277 who had a singleton pregnancy. In total, six abortions occurred before 16 weeks gestation. In the selected 0.25 mg dose group (containing 25 pregnant subjects), two abortions occurred. Karyotyping of the abortion material in one of the abortions identified trisomy 18 (Edwards syndrome).

Of the 61 subjects with an ongoing pregnancy, two subjects with singleton pregnancies did not give birth to a live-born infant. One subject aborted in week 19 and one subject experienced a fetal death in utero in week 27. Of the 5 initial triplets, 4 triplets were reduced to twins by selective or spontaneous reduction. Of the 11 twins, 2 twins spontaneously reduced to singletons.

In total, 73 infants, 33 boys and 40 girls, were born. Physical abnormalities were noted at birth in 9 babies, 8 diverse minor abnormalities and 1 major abnormality (Beckwith Wiedemann syndrome characterized by exomphalos and macroglossia). Ganirelix appears to be safe for the off-spring of subjects treated with the drug.

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F. Literature Survey:

Information is provided on expectations of clinical outcome from subjects undergoing controlled ovarian hyperstimulation with and without pituitary suppression. For results without pituitary suppression, data was obtained from 5 to 12 publications and for results with pituitary suppression, data was obtained from 3 to 5 publications. Table 29 lists overall rates for pertinent endpoints.

Table 29
Overall Rates of Selected Clinical Endpoints

		Without Suppression	With Suppression
Incidence of OHSS	(%/Attempt)	0.9	3.4
Clinical Pregnancy	(%/Attempt)	16.5	31.1
Spontaneous Abortion	(%/Clinical Pregnancy)	21.7	23.3
Multiple Pregnancy	(%/Pregnancy)	24.5	35.0
Live Birth	(%/Attempt)	12.6	23.7

The clinical pregnancy rate and live birth rate have clearly been improved with the use of Gn-Rh agonists for pituitary suppression. The spontaneous abortion rate is the same for both regimens. Unfortunately, the multiple pregnancy rate is considerably higher with the use of Gn-RH agonists and the incidence of ovarian hyperstimulation syndrome is somewhat higher with the use of Gn-RH agonists.

The United States IVF Registry was established as a collaborative effort between the Society of Assisted Reproductive Technology (SART) of the American Fertility Society and Medical Research International and it monitors virtually all of the ART practiced in the United States. Of 7,565 stimulation cycles reported to it in 1990 via "Recordkeeper", a computer based system designed for recording patient information for ART, 5,859 (77%) included use of a Gn-RH agonist. There were 1299 canceled cycles reported with a cancellation rate of 14% in cycles with a Gn-RH agonist and 26% in those without. (18,179 stimulation cycles were reported via paper data form and tne number that included use of Gn-RH agonist is unknown). This indicates that the cancellation rate using a

Gn-RH agonist is about half that without the use of one.

Reviewer's Comments:

Since 1990, the use of a Gn-RH agonist in ART has steadily increased from 77% of stimulation cycles to 97% of stimulation cycles. One can argue as to why this is so, but it is now part of the standard of care in the practice of medicine. The literature clearly indicates that the use of a Gn-RH agonist in women undergoing controlled ovarian hyperstimulation results in approximately a doubling of the clinical pregnancy and live birth rates. This improved outcome is directly related to the fact that the use of a Gn-RH agonist results in a cancellation rate half that of when an agonist is not used. The lower cancellation rate is directly related to the decreased occurrence of premature LH surges associated with the use of Gn-RH agonists.

IX. Postmarketing Clinical Studies:

No postmarketing clinical trials are required.

X. Safety Update:

A 90-day safety update was submitted April 27, 1999. The report covers the time period September 1, 1998 to January 28, 1999.

No long-term effects of treatment with ganirelix have been reported.

Safety data from study has been integrated with studies 38602 and 38607 and results (disposition, demographics, drug exposure, adverse events, local tolerance, clinical laboratory parameters, and vital signs) reanalyzed and show that ganirelix continues to be well-tolerated and safe when administered at a dose of 0.25 mg per day.

No new safety concerns are apparent. The incidence of common adverse events with an incidence ≥1% in ganirelix subjects remains essentially unchanged except for the addition of one event, injection site pain, with an incidence of 1.7%. The total incidence of OHSS for ganirelix is 3.1% and 5.9% for buserelin. The incidence of mild cases for ganirelix is 1.4% and 1.7% for buserelin. The incidence of moderate cases for ganirelix is 1.1% and 4.2% for buserelin. The incidence of severe cases of OHSS for ganirelix is 0.6% (6 cases). Severe OHSS did not occur in any of the 23 subjects treated with buserelin.

XI. Reviewer's Overall Evaluation and Conclusions:

Antagon is a Gn-RH antagonist that was developed for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation for which Gn-RH agonists are currently generally accepted around the world as being effective as an aid in improving results of in-vitro fertilization procedures.

The use of Gn-RH agonists for controlled ovarian hyperstimulation has specific disadvantages such as the initial stimulation of gonadotropin release (flare-up) in long protocols, the long period to achieve effective pituitary suppression, and possibly a somewhat higher dose of FSH required for controlled ovarian hyperstimulation due to suppression of endogenous FSH. Gn-RH antagonists, however, suppress gonadotropins immediately by blocking the Gn-RH receptor and need be administered during the short period of time when premature LH surges are likely to occur.

Many Gn-RH antagonists have been studied for many years, but were found to cause hypersensitivity reactions due to direct activation of mast cells resulting in the release of various mediators, in particular histamine. Antagon, as a new third generation antagonist, was found to have significantly reduced histamine-releasing capacity in in-vitro studies. In pre-clinical studies, administration of Antagon resulted in rapid, profound, reversible suppression of the pituitary-gonadal axis with minimal histamine releasing properties. Antagon, thus far in clinical trials, has been well tolerated by humans. Analysis of anti-Antagon antibody formation in study 38608 completed thus far have been negative for total Ig and IgE anti-Antagon antibodies. Hypersensitivity problems are not anticipated with Antagon.

Although Gn-RH agonists are widely used "off label" in this country for the prevention of LH surges in women undergoing controlled ovarian hyperstimulation, no Gn-RH agonist is approved for this indication in the United States. There is, as yet, no Gn-RH antagonist approved for this indication in any country.

Two completed, controlled, multicenter, randomized trials and one follow-up study provided the bulk of the evaluable data in this application. A total of 794 subjects received Antagon at any dose including 532 subjects who received Antagon at the recommended, selected dose of 0.25 mg. Studies 38602 and 38607 were pivotal studies. Subjects were treated for one cycle only. Subjects excluded from study included those with a history of/or current endocrine abnormality such as polycystic ovary syndrome, a history of no or low ovarian response to FSH/hMG treatment, subjects with known hypersensitivity to GnRH or its analogs, and subjects with type I hypersensitivity (urticaria, eczema, hay fever, asthma, house dust, etc.) Subjects were 18-39 years of age and were female partners of infertile couples for whom controlled ovarian hyperstimulation and in-vitro fertilization with or without intracytoplasmic sperm injection was indicated. Subjects weighed between 110-165 pounds.

Study 38602 was a dose-finding study designed to select the minimal effective dose of Antagon in preventing premature surges of endogenous luteinizing hormone in women undergoing controlled ovarian hyperstimulation with recombinant follicle-stimulating hormone. The 0.25 mg dose was determined to be the minimal effective dose. Of 70 subjects who received the 0.25 mg dose, only three did not receive an hCG injection. Subject 0023 had insufficient ovarian response and subjects 0180 and 0231 had risks for hyperstimulation. The remaining 67 subjects (95.7%) had oocyte retrievals while 4.3% of subjects did not because of cycle cancellation for valid reasons. The 4.3% cancellation rate is an extremely low and desirable rate. The 0.25 mg dose was determined to be safe, well-tolerated, and prevented LH rises in women undergoing controlled ovarian hyperstimulation. Pregnancies occurring in the study were followed-up in study 38603.

Study 38607 was the pivotal study demonstrating the efficacy and safety of ganirelix in women undergoing controlled ovarian hyperstimulation using a long protocol of buserelin as a reference treatment. Buserelin is a Gn-RH agonist which has been widely used in Europe for many years to prevent LH surges in women undergoing controlled ovarian hyperstimulation. Buserelin is not available in the United States. Buserelin was chosen as the reference treatment because there is no other Gn-RH antagonist available that could be used for this purpose and buserelin is widely used in Europe for this indication where this study was conducted. No agonist is approved in the United States for this indication.

A total of 486 subjects were randomized to the ganirelix arm and 244 subjects to the buserelin arm. A total of 463 ganirelix subjects and 238 buserelin subjects received either recombinant FSH or Gn-RH analog treatment and were included in the AST and ITT analyses. In the ganirelix arm, a total of 448 subjects received hCG, 440 had oocyte retrieval, 399 had embryo transfer, and 94 had vital pregnancies. In the buserelin arm, 224 subjects received hCG, 221 had oocyte retrieval, 208 had embryo transfer, and 61 had vital pregnancies. A number of efficacy end points were investigated and compared. Results are shown in Table 30. Generally, the combination of efficacy, safety, and convenience of ganirelix is not clinically inferior to buserelin.

Table 30

Summary Results of Study 38607

Parameter Studied	Ganirelix	Buserelin
Duration of Study Drug Treatment	5.4 days	27.2 days
Duration of FSH Treatment	9 days	10 days
Total FSH Dose	1500 IU	1800 IU
Treatment Failures	3.5%	5.9%
Ovarian Hyperstimulation	2.4%	5.9%
Number of cumulus-oocyte-complexes	8.7	9.7
Number of good quality embryos	3.3	3.5
LH $\geq$ 10 IU/mL	2.8%	1.3%
Clinical Pregnancies	21.8%	28.2%
Ongoing Pregnancy Rate	20.3%	25.7%

The major advantage of ganirelix treatment is patient convenience and potentially less treatment cost since the overall duration of ganirelix treatment is considerably less than the overall duration of buserelin treatment, the mean duration of FSH treatment when ganirelix is given is one day less than when buserelin is given, and the total dose of FSH per treatment cycle is 300 IU less when ganirelix is given than when buserelin is given. Treatment failures are less with ganirelix than with buserelin and the ovarian hyperstimulation syndrome occurs less frequently with ganirelix treatment than with buserelin treatment. In other efficacy parameters, such as the number of oocytes, number of good quality embryos, number of mature follicles before hCG, and ongoing pregnancy rate, buserelin appears to be somewhat superior to ganirelix. Overall, ganirelix is safe, convenient, and effective for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation. It is impossible, however, to totally isolate the efficacy of ganirelix from the efficacy of the entire complex in-vitro fertilization treatment regimen.

Study 38603 was a followup of pregnancies that occurred in subjects participating in study 38602. Pregnancy outcome data was collected for 67 subjects. Of 73 infants born, one major physical abnormality was noted (Beckwith Wiedemann syndrome). These results suggest that ganirelix is safe for the off-spring of subjects treated with the drug.

Study 38607 demonstrates that ganirelix is not clinically inferior to buserelin, but one may wonder if agonists, such as buserelin, or antagonists, such as ganirelix, add any value to controlled ovarian hyperstimulation treatment over the use of conventional stimulation regimens only. The overwhelming preponderance of evidence, taken as a whole, is in favor of agonists being advantageous in this regard, but the scientific literature contains reports of many less than perfect studies. Some prospective studies were non-randomized. Some studies were retrospective. Many studies included subjects who were poor responders in previous treatment cycles. The results of prospective, randomized studies have been contradictory. Although some studies have reported significantly increased pregnancy rates with the use of agonists, other studies have suggested that there is no obvious superiority of regimens incorporating agonists over conventional stimulation protocols.

A 1992 randomized study of 81 subjects by
concluded that the routine use of Gn-RH agonists for all patients undergoing in-vitro fertilization had practical, but no significant medical advantages.

A 1991 randomized study of 93 subjects by
concluded that the major advantage of Gn-RH agonists over non-GnRH agonist protocols was in decreasing the cancellation rate and increasing the number of oocytes and concepti obtained.

A 1990 randomized study of 90 subjects by concluded that the use of an agonist resulted in a reduced incidence of inadequate responses, an absence of premature luteinization, a greater number of oocytes per retrieval and a higher pregnancy rate per oocyte retrieval.

A 1992 report of a retrospective file review by of 365 patients treated with hMG alone and 393 patients treated with an agonist followed by hMG stimulation concluded that use of an agonist reduced the cancellation rate, increased the number of retrieved oocytes, and resulted in a higher pregnancy rate (15.5% with agonist and 12.6% with hMG alone.)

A 1992 retrospective evaluation of 188 patients by concluded that adding a Gn-RH agonist significantly improved the number of oocytes harvested and the viable pregnancies per transfer and reduced spontaneous abortions, but found no difference in the fertilization, implantation, and delivery rates per embryo transfer.

A 1991 randomized study of 276 patients by concluded that the use of an agonist resulted in a considerably reduced cancellation rate, increased number of oocytes, more embryos per retrieval, and a significantly higher pregnancy rate per cycle.

The above studies, when evaluated together, indicate that the use of an agonist does result in a reduced cancellation rate, an increase in the number of oocytes, and an increase in the pregnancy rate. Agonists do add value to controlled ovarian hyperstimulation treatment. Even though concluded that the routine use of an agonist had no significant medical advantages, some comments on his data are pertinent. The cancellation rate in the 3 day agonist plus hMG arm was 10.81% while the cancellation rate in the hMG alone arm was 13.58%. The mean number of embryos cleaved was 3.26 in the agonist plus hMG arm and 2.54 in the hMG alone arm. When the two treatment arms that did not utilize an agonist are added together and compared to the two treatment arms that did utilize an agonist added together, the pregnancy rate per cycle, pregnancy rate per embryo transfer, live birth rate per cycle, and live birth rate per embryo transfer are all higher in the agonist plus hMG group than in the group that did not utilize an agonist.

The use of buserelin, an agonist not available in the United States, but widely used in Europe (registered in Finland, France, Sweden, Israel, the Netherlands, and the United Kingdom) for the prevention of premature LH surges in women undergoing controlled ovarian hyperstimulation, was a scientifically rational choice as a reference to which ganirelix was compared in study 38607. There is no antagonist marketed anywhere in the world that could have been used in its stead. If one accepts the premise, as I do, that buserelin is effective for reducing the incidence of premature LH surges, then one should accept the conclusion that ganirelix acetate is also effective in reducing the incidence of premature LH surges.

Historically, one can make a valid case for the efficacy of agonists in reducing the incidence of premature LH surges. The sponsor submitted 12 reports published between 1990 and 1995 of reported clinical pregnancy rates per attempted cycle after controlled ovarian hyperstimulation with gonadotropins only. The overall mean clinical pregnancy rate, based on 1292 women, is 16.5% with a range of 0-25%. The sponsor submitted 5 reports published between 1994 and 1997 of reported clinical pregnancy rates per attempted cycle after controlled ovarian hyperstimulation utilizing Gn-RH agonists for down-regulation. The overall mean clinical pregnancy rate based on 853 women is 31.1% with a range of 19-45%.

The clinical pregnancy rate of 23.3% found in study 38607 with ganirelix is 41% higher than the mean clinical pregnancy rate of 16.5% found when gonadotropins only are used.

The sponsor submitted 10 reports published between 1990 and 1995 of reported live birth rates per attempted cycle after controlled ovarian hyperstimulation with gonadotropins only. The overall mean live birth rate, based on 1062 women, is 12.6 with a range of 0-25. The sponsor submitted five reports published between 1994 and 1997 of reported live birth rates per attempted cycle after controlled ovarian hyperstimulation utilizing Gn-RH agonists for down-regulation. The overall mean live birth rate, based on 853 women is 23.7% with a range of 15-34%. The live birth rate of 31.4% found in study 38602 with ganirelix is 2.5 times that found when an agonist or antagonist is not used. This is strong evidence of the efficacy of ganirelix. There is a small possibility, of course, that the difference in live birth rates may be accounted for by an "ecological fallacy". The difference could be due to one or more factors other than ganirelix as the underlying reason for the vast difference, but this is highly unlikely since the live birth rate is based on individual births. The use of ganirelix is, however, only a small part of the entire in-vitro fertilization procedure.

Hughes in a meta-analysis of ten clinical trials published in 1992 concluded that the weight of published data indicated that Gn-RH agonists increased the clinical pregnancy rate per cycle and per embryo transfer and significantly reduced the cycle cancellation rate.

There is additional historical data demonstrating the efficacy of agonists where there is much less risk of an "ecological fallacy" having occurred. In 1990, of 7,565 ART stimulation cycles reported to SART, 5,859 (77%) included use of a Gn-RH agonist. There were 1299 canceled cycles reported with a cancellation rate of 14% in cycles with a Gn-RH agonist and 26% in cycles without an agonist. The cancellation rate using an agonist is almost half that without the use of one. The lower cancellation rate is directly related to the decreased incidence of premature LH surges associated with the use of Gn-RH agonists. It is not related to a growing experience with and improved quality of assisted reproductive technology since all of the cycle data reported occurred at one point in time, the year 1990.

Other historical data that is relevant was obtained from a review of some of the annual SART data which is data reported for all ART stimulation cycles, including IVF cycles, that were initiated in the United States and Canada. In 1988, 41% of clinics reported administering a Gn-RH analog as part of their most commonly used stimulation regimens. In 1989, 73% of clinics were utilizing a Gn-RH analog as part of their stimulation regimens and in 1990 fully 97% of clinics were utilizing a Gn-RH analog as part of their stimulation regimens.

Table 31 is data extracted from annually reported SART data giving the year, the overall cancellation rate reported for that year and the overall clinical pregnancy rate per embryo transfer reported for that year for IVF stimulation cycles. Data beyond the year 1995 has not been published as yet.

Table 31
IVF Stimulation Cycles (SART Data)

Year	Cancellation Rate %	Clinical Pregnancies per E.T. (%)
1988	28.0	19.0
1989	19.0	21.0
1990	14.0	22.0
1992	15.0	24.1
1993	14.0	25.9
1994	13.8	29.1
1995	14.2	30.7

The cancellation rate has decreased from 28% in 1988 when 41% of clinics were utilizing Gn-RH analogs to 14% in 1990 when 97% of clinics were utilizing Gn-RH analogs. During the same time period clinical pregnancies per embryo transfer increased from 19% in 1988 to 22% in 1990. At that point progressively more stimulation cycles in each clinic included utilization of Gn-RH agonists and the clinical pregnancy rate per embryo transfer continued to increase progressively from 24.1% in 1992 to 30.7% in 1995, while at the same time cancellation rates have remained relatively stable. These changes in cancellation rates and clinical pregnancy rates are attributed to the use of Gn-RH agonists. The cycle cancellation rates in studies 38602 and 38607 are lower than those reported to SART with the use of agonists. The SART data shows that while cancellation rates were decreased by 50% from 1988 to 1995, the clinical pregnancy rates have increased 62% in 1995 from that in 1988. These changes over time in cancellation rates and clinical pregnancy rates are clinically significant and were due in large part, if not entirely, to the utilization of Gn-RH agonists in the stimulation regimens.

Ganirelix is well-tolerated and safe. Adverse events are not a problem. No clinically relevant drug-related trends for laboratory parameters or vital signs were identified. Anti-ganirelix antibodies were not detected in the post-treatment sera of any subject in whom they were tested (163 first treatment cycles, 77 second treatment cycles and 30 third treatment cycles). Based on the birth of 73 infants and their follow-up, ganirelix appears to have no deleterious effects on the offspring of subjects treated with the drug.

XII. Labeling:

Revised draft labeling submitted June 9, 1999 is currently being revised by the sponsor as suggested by us.

XIII. Recommendation:

Approval of the application is recommended.

/S/

Ridgely C. Bennett, M.D., M.P.H.

I concur

/S/

-, MD, Ph.D.
6/15/99